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For Hand Delivei

June 6, 2007

TSCA Document Control Office (7407M)
ATTN: TSCA Section 8(e) Coordinator
EPA East Building, Room 6428
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Avenue, NW
Washington, DC 20460-0001

CONTAIN NO CBI

Re: TSCA Section 8(e) Substantial Risk Notification for Draft Reproductive/Developmental Toxicity Data from a draft OECD 422 Oral Combined Repeat Dose Study on 1,5-Cyclooctadiene

Dear Sir:

INVISTA is submitting draft results from a draft sub-chronic, OECD 422 study on 1,5-Cyclooctadiene (COD), CASRN 111-78-4, conducted by SafePharm Labs in the UK.

COD was administered by gavage to three groups each of ten male and ten female Sprague-Dawley rats, for up to fifty-four consecutive days, at dose levels of 50, 175 and 600 mg/kg/day. A control group of ten males and ten females was dosed with vehicle alone (Dried Arachis oil). Two recovery groups, each of five males and five females, were treated with the high dose (600 mg/kg/day) or the vehicle alone for forty-two consecutive days and then maintained without treatment for a further fourteen days.

Treatment-related effects on reproduction were observed as a reduced offspring bodyweight and subsequent reduced mean litter weights on Days 1 and 4 *post partum* for litters treated with 600 mg/kg/day together with a reduction in mean bodyweight gain between Days 1 and 4 *post partum*. No such effects were detected at 175 or 50 mg/kg/day. Therefore the "No Observed Effect Level" (NOEL) for reproductive toxicity was considered to be 175 mg/kg/day.

These findings do not necessarily indicate that 1,5-Cyclooctadiene is a specific reproductive or developmental toxicant. Although slight maternal toxicity is apparent at the high dose, EPA guidelines generally require reporting of Reproductive/Developmental effects at any dose regardless of the presence of maternal toxicity.

The above information is from a draft study that has not yet been completed. INVISTA will submit the final version of the study to EPA when it becomes available.

INVISTA™

This report is being submitted in accordance with TSCA Section 8(e) guidance. Please do not hesitate to contact me if you have any questions. I may be reached at (316) 828-1470.

Sincerely,

Betsy Duncan

Betsy Duncan
TSCA Program Manager
Environmental Health and Safety

DRAFT REPORT

1,5-CYCLOOCTADIENE(COD):

ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

SPL PROJECT NUMBER: 2231/0007
SAFEPHARM LABORATORIES

SafePharm Laboratories

1,5-CYCLOOCTADIENE (COD):

ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

SPL PROJECT NUMBER: 2231/0007

AUTHORS: J S Dunster
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QUALITY ASSURANCE REPORT

The conduct of this study has been subjected to periodic inspections by Safepharm Quality Assurance Unit.

This report has been audited by Safepharm Quality Assurance Unit, and is considered to be an accurate account of the data generated and of the procedures followed.

Unless otherwise indicated, the outcome of QA evaluation is reported to the Study Director and Management on the day of evaluation. Audits of study documentation and inspections were as follows:

	20 July 2006	Protocol Compliance Audit
	30 August 2006	Pairing
	11 September 2006	Test Material Preparation
	29 September 2006	Dosing
	28 September 2006	Parental Observations
	29 September 2006	Animal Preparation
	28 September 2006	Litter Observations
	28 September 2006	Post Mortem
ϕ	29 November 2006	Histology (reported to management on 04 December 2006)
	16 April 2007	Draft Report Audit
	Date of QA Signature	Final Report Audit

ϕ Audit by Propath UK Ltd QAU

..... DATE: .....

For Safepharm Quality Assurance Unit*

***Authorised QA Signatures:**

Head of Department:	JR Pateman CBiol MIBiol DipRQA FRQA
Deputy Head of Department:	JM Crowther MIScT MRQA
Senior Audit Staff:	JV Johnson BSc MRQA; G Wren ONC MRQA

GLP COMPLIANCE STATEMENT (OECD)

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106 as amended by SI 2004/0994)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 2004/9/EC and 2004/10/EC.

These international standards are acceptable to the Regulatory agencies of the following countries: Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Republic of Korea, Luxembourg, Mexico, The Netherlands, New Zealand, Norway, Poland, Portugal, Slovenia, South Africa, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the United States of America.

This report fully and accurately reflects the procedures used and data generated.

..... DATE: .....

J S Dunster BSc (Hons)
Study Director

The following scientific and supervisory personnel were involved in the study under the overall supervision of the Study Director:

N Szysler HNC
J Harvey
J Kemp

AUTHENTICATION

The microscopic pathology data presented in this report were compiled by me and the results reported herein accurately reflect the data obtained.

..... DATE: .....

P N Brooks MSc BSc EurProBiol CBiol MIBiol
EUROTOX Registered Toxicologist
Study Pathologist

The analytical data presented in this report were compiled by me or under my supervision and the results reported herein accurately reflect the data obtained.

..... DATE: .....

P Watson
Laboratory Supervisor
Analytical Services

Approved for issue:

..... DATE: .....

E Wood CBiol MIBiol
Head of Toxicology

CONTENTS

PART 1: ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

1,5-CYCLOOCTADIENE (COD):

ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

SUMMARY

Introduction. The study was designed to investigate the systemic toxicity and potential adverse effects on reproduction (including offspring development) of the test material and complies with the recommendations of the OECD Guidelines for Testing of Chemicals No. 422 "Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test" (adopted 22 March 1996) and US EPA Guideline 870.3650, July 2000.

Methods. The test material was administered by gavage to three groups each of ten male and ten female Sprague-Dawley Crl:CD® (SD) IGS BR strain rats, for up to fifty-four consecutive days, at dose levels of 50, 175 and 600 mg/kg/day. A control group of ten males and ten females was dosed with vehicle alone (Dried Arachis oil). Two recovery groups, each of five males and five females, were treated with the high dose (600 mg/kg/day) or the vehicle alone for forty-two consecutive days and then maintained without treatment for a further fourteen days.

Clinical signs, behavioural assessments, bodyweight development and food and water consumption were monitored during the study. Haematology and blood chemistry were evaluated prior to mating on five selected non-recovery males and non-recovery females from each dose group.

Pairing of non-recovery animals within each dose group was undertaken on a one male: one female basis on Day 15 of the study, to produce litters.

During the lactation phase, daily clinical observations were performed on all surviving offspring, together with litter size, offspring weights and assessment of developmental landmarks.

Extensive functional observations were performed on five selected parental males from each dose group after the completion of the mating phase, and for five selected parental females from each dose group on Day 4 *post partum*.

Non- recovery males were terminated on Day 43, followed by the termination of all surviving non-recovery females and offspring on Day 5 *post partum*. Haematology and blood chemistry was also evaluated at termination on five selected non-recovery males and non-recovery females

from each dose group at the end of the treatment period and for all recovery group animals at the end of the treatment free period. All animals were subjected to a gross necropsy examination and histopathological evaluation of selected tissues was performed.

Results.

Mortality. One control female was killed *in extremis* due to difficulties during parturition. There were no further unscheduled deaths.

Clinical Observations. Animals of either sex treated with 600 mg/kg/day showed increased salivation from Day 1 (males) and Day 5 (females) onwards. Episodes of hunched posture, ataxia, generalised red/brown fur staining, wet fur and orange staining on cage tray liners were evident in animals of either sex treated with 600 mg/kg/day throughout the treatment period. Isolated instances of lethargy, tiptoe gait and increased lachrymation (females only) were also evident at this treatment level. Animals of either sex treated with 175 mg/kg/day showed increased salivation from Day 7 (males) onwards and Day 13 (females). Males treated with 175 mg/kg/day also showed orange staining on cage tray liners during the first two weeks of treatment and ataxia on Days 39 and 40. Males treated with 50 mg/kg/day showed instances of increased salivation from Day 8 onwards and red/brown stained fur on Day 39. No such effects were detected in females treated with 50 mg/kg/day.

Behavioural Assessments. Open field assessments in animals of either sex confirmed the signs of increased salivation, hunched posture, tiptoe gait, and ataxia (females only) detected at 600 mg/kg/day throughout the treatment period. No such effects were detected in animals of either sex treated with 175 or 50 mg/kg/day.

Functional Performance Tests. No treatment-related effects were detected.

Sensory Reactivity Assessments. No treatment-related effects were detected.

Bodyweight. Males treated with 600 mg/kg/day showed a reduction in bodyweight gain during Weeks 1, 2, 4 and 6. Females treated with 600 mg/kg/day showed a slight reduction in bodyweight gain during Week 2 of maturation. No adverse effect on bodyweight gain was detected for males treated with 175 or 50 mg/kg/day throughout the treatment period or for females treated with 175 or 50 mg/kg/day throughout the two week maturation period. There was no adverse effect on bodyweight gain for females during the gestation or lactation phase of the study.

Food Consumption. No adverse effect on food consumption was detected for males throughout the treatment period or for females throughout the two week maturation period. There were no adverse effects on food consumption for females during the gestation or lactation phases of the study. A slight reduction in food efficiency was detected for males treated with 600 mg/kg/day during Week 6 and for females from this treatment group during Week 2 of maturation. No such effects in food efficiency were detected in animals of either sex treated with 175 or 50 mg/kg/day.

Water Consumption. Animals of either sex treated with 600 mg/kg/day showed an increase in water consumption from Day 8 of maturation onwards. This effect continued throughout gestation for 600 mg/kg/day females. No such effects were detected in animals of either sex treated with 175 or 50 mg/kg/day.

Haematology. No treatment-related effects were detected.

Blood Chemistry. No treatment-related effects were detected.

Urinalysis. No treatment-related effects were detected.

Reproductive Screening:

Mating. There were no treatment-related effects on male or female mating or conception rates. The distribution of pre-coital intervals for treated animals was comparable to controls.

Gestation. There were no differences in gestation lengths. The distribution for treated females was comparable to controls.

Offspring Litter Size and Viability. There were no treatment-related effects on litter size or offspring viability.

Offspring Growth and Development. Mean offspring bodyweight and subsequent mean litter weights were reduced on Day 1 and 4 *post partum* for female litters treated with 600 mg/kg/day. A reduction in mean offspring bodyweight gain was also detected for these litters between Days 1 and 4 *post partum*. No such effect on offspring growth was detected from female litters treated with 175 or 50 mg/kg/day. No treatment-related effects on offspring development were detected.

Offspring Observations. No clinically observable signs of toxicity were detected for offspring from any treatment groups.

Pathology:

Necropsy. No treatment-related macroscopic abnormalities were detected for adults or offspring.

Organ Weights. Non-recovery females treated with 600 mg/kg/day showed a statistically significant increase in liver weight both absolute and relative to terminal bodyweight. Recovery females continued to show elevated relative liver weights following fourteen days without treatment. No such effects were detected in males treated with 600 mg/kg/day or animals of either sex treated with 175 or 50 mg/kg/day.

Uterine Examination. No treatment-related effects were detected.

Histopathology. The following treatment-related microscopic changes were detected:

LIVER: Centrilobular hepatocyte enlargement was observed in relation to treatment for females treated with 600 mg/kg/day but not at any other dose level. Males were not similarly affected. Only three animals were affected to a minimal severity and this was considered to be a marginal response to treatment.

THYROID: Follicular cell hypertrophy was observed as an effect of treatment for females treated with 600 mg/kg/day but probably not at any other treatment level. Males were not similarly affected, the group distribution of the lesion being more variable.

OESOPHAGUS: A higher incidence of mononuclear cell infiltration in the peripheral musculature was observed among females treated with 600 and 175 mg/kg/day.

Conclusion. The oral administration of 1,5-Cyclooctadiene (COD) to rats by gavage at dose level of 600, 175 and 50 mg/kg/day resulted in treatment-related changes in males treated with 600 mg/kg/day and in females treated with 600 and 175 mg/kg/day. The 'No Observed Effect Level' (NOEL) was therefore considered to be 175 mg/kg/day for males and 50 mg/kg/day for females.

Slight bodyweight reductions and increased water consumptions detected in animals of either sex treated with 600 mg/kg/day were considered not to represent "serious damage" to health as defined by the criteria given in the EC labelling guide of Commission Directives 2004/9/EC and 2004/10/EC. The microscopic changes observed in females at 600 and 175 mg/kg/day were regarded as adaptive in nature or as a common result from the physical trauma of gavage dosing. The "No Observed Adverse Effect Level" (NOAEL) for either sex was therefore considered to be 600 mg/kg/day.

Treatment-related effects on reproduction were observed as a reduced offspring bodyweight and subsequent mean litter weights on Days 1 and 4 *post partum* for litters treated with 600 mg/kg/day together with a reduction in mean bodyweight gain between Days 1 and 4 *post partum*. No such effects were detected at 175 or 50 mg/kg/day, therefore the "No Observed Effect Level" (NOEL) for reproductive toxicity was considered to be 175 mg/kg/day.

1,5-CYCLOOCTADIENE (COD):

ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

1. INTRODUCTION

The study was performed according to the protocol presented in Appendix 21 and was designed to investigate the systemic toxicity of the test material and potential adverse effects on reproduction, including offspring development, by repeated oral administration to the Sprague-Dawley Crl:CD® rat for up to fifty four consecutive days, at dose levels of 50, 175 and 600 mg/kg/day.

The study was designed to comply with the OECD Guidelines for Testing of Chemicals, No. 422: "Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test" (adopted 22 March 1996) and US EPA Guideline 870.3650, July 2000.

The rat was selected for this study, as it is a readily available rodent species historically used in safety evaluation studies and is acceptable to appropriate regulatory authorities.

The dose levels were chosen based on the results of the range-finder presented in Part 2 of this report. The oral route was selected as the most appropriate route of exposure, based on the physical properties of the test material, and the results of the study are believed to be of value in predicting the likely toxicity of the test material to man and to screen for potential adverse effects on reproduction.

The study was performed between 17 July 2006 and 12 January 2007.

2. TEST MATERIAL AND EXPERIMENTAL PREPARATION

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	1,5-Cyclooctadiene (COD)
Description	:	Colourless liquid
Purity	:	99%
Batch number	:	06010MD
Date received	:	12 June 2006/ 21 July 2006 / 10 August 2006
Storage conditions	:	Room temperature in the dark

The integrity of supplied data relating to the identity, purity and stability of the test material is the responsibility of the Sponsor.

2.2 Preparation of Test Material

For the purpose of the study, the test material was prepared at the appropriate concentrations as a suspension in Dried Arachis oil. The stability and homogeneity of the test material formulations were determined by Safepharm Analytical Laboratory as part of this study. Results are given in Appendix 23 and show the formulations to be stable for at least fourteen days. Formulations were therefore prepared weekly and stored at approximately +4°C in the dark.

Samples were taken of each test material formulation and were analysed for concentration of 1,5-Cyclooctadiene (COD) at Safepharm Analytical Laboratory. The method used for analysis of formulations and the results obtained are given in Appendix 23. The results indicate that the prepared formulations were within ±5% of the nominal concentration.

3. METHODS

3.1 Animals and Animal Husbandry

A sufficient number of male and female Sprague-Dawley Crl:CD (SD) IGS BR strain rats were obtained from Charles River (UK) Limited, Margate, Kent. On receipt, the animals were examined for signs of ill-health or injury. The animals were acclimatised for 7 days, during which time their health status was assessed. A total of 100 animals (50 males and 50 females) were accepted into the study. At the start of treatment, the males weighed 274 to 334g, the females weighed 161 to 204g and were approximately eight weeks old.

Initially, all animals were housed in groups of five in polypropylene cages with stainless steel grid floors and tops, suspended over polypropylene trays lined with absorbent paper. During the mating phase, animals were transferred to similar cages on a one male: one female basis. Following evidence of successful mating, the males were returned to their original cages. Mated females were housed individually during gestation and lactation, in polypropylene cages with solid floors and stainless steel lids, furnished with softwood flakes (Datesand Ltd. Cheshire, UK).

The animals were allowed free access to food and water. A pelleted diet (Rodent PMI 5002 (Certified) diet, BCM IPS Limited, London, UK) was used throughout the treatment period. A certificate of Analysis of the batch used is given in Appendix 22. Mains drinking water was supplied from polycarbonate bottles attached to the cage. The diet and drinking water were considered not to contain any contaminant at a level that might have affected the purpose or integrity of the study. Environmental enrichment was provided in the form of wooden chew blocks (B & K Universal Ltd, Hull, UK) and cardboard fun tunnels (Datesand Ltd, Cheshire, UK)

except for mated females during gestation and lactation. Mated females were also given softwood flakes, as bedding, throughout gestation and lactation.

The animals were housed in air-conditioned rooms within the Safepharm Laboratories Limited Barrier Maintained Rodent Facility. The rate of air exchange was at least fifteen air changes per hour and the low intensity fluorescent lighting was controlled to give twelve hours continuous light and twelve hours darkness. Environmental conditions were continuously monitored by a computerised system and print-outs of hourly mean temperatures and humidities are included in the study records. The temperature and relative humidity controls were set to achieve target values of 21±2°C and 55 ±15% respectively. Deviations from these targets were considered not to affect the purpose or integrity of the study.

The animals were allocated to dose groups using a randomisation procedure based on stratified bodyweights and the group mean bodyweights were then determined to ensure similarity between the dose groups. The animals were uniquely identified within the study, by an ear punching system routinely used in these laboratories.

3.2 Procedure

Animals were allocated to treatment groups as follows:

Treatment Group	Dose Level (mg/kg/day)	Treatment Volume (ml/kg)	Concentration (mg/ml)	Animal Numbers	
				Male	Female
Control	0	4	0	(1 - 10)	(11 - 20)
Recovery Control	0	4	0	(81 - 85)	(86 - 90)
Low	50	4	12.5	(21 - 30)	(31 - 40)
Intermediate	175	4	43.8	(41 - 50)	(51 - 60)
High	600	4	150	(61 - 70)	(71 - 80)
Recovery High	600	4	150	(91 - 95)	(96 -100)

The numbers in parentheses ( ) show the individual animal numbers allocated to each treatment group.

The test material was administered daily (except for females during littering/parturition) by gavage using a stainless steel cannula attached to a disposable plastic syringe. Control animals were treated in an identical manner with 4 ml/kg/day of Dried Arachis oil. Recovery group animals were maintained for a further fourteen days treatment free period following termination of treatment.

The volume of test and control material administered to each animal was based on the most recent bodyweight and was adjusted weekly for non-recovery males, recovery animals and non-recovery

females during maturation and on Days 0, 7, 14 and 20 of gestation and on Days 1 and 4 of lactation.

Chronological Sequence of Study

i) Groups of ten male and ten female animals were treated daily at the appropriate dose level throughout the study (except for females during parturition where applicable).

ii) Prior to the start of treatment and once weekly, all animals were observed for signs of functional/behavioural toxicity.

iii) One day prior to pairing (Day 14), blood samples were taken from the first five non-recovery males and the first five non-recovery females, from each dose group and analysed for haematological and blood chemical parameters.

iv) On Day 15, all animals (excluding Recovery animals) were paired on a 1 male:1 female basis within each dose group for a maximum of fourteen days.

v) Following evidence of mating using vaginal smearing, the males were returned to their original cages and females were transferred to individual cages.

vi) On completion of mating (during Week 6), five selected non-recovery males per dose group were evaluated for functional/sensory responses to various stimuli.

vii) Pregnant females were allowed to give birth and maintain their offspring until Day 4 *post partum*. Evaluation of each litter size, litter weight, mean pup weight, clinical observations and landmark developmental signs were also performed during this period.

viii) At Day 4 *post partum*, five selected females per dose group were evaluated for functional/sensory responses to various stimuli.

ix) Following completion of the female gestation and lactation phases, the male dose groups were killed and examined macroscopically on Day 43. Blood chemical and haematological assessments were performed on five selected non-recovery males from each dose group. During the final week urinalysis was performed on five selected non-recovery males from each dose group.

x) At Day 5 *post partum*, all surviving females and offspring were killed and examined macroscopically and blood chemical and haematological assessments were performed on five females from each dose group.

xi) Urinalysis was performed on Recovery Males during the final week of the recovery period.

3.3 Observations

3.3.1 Clinical Observations

All animals were examined for overt signs of toxicity, ill-health and behavioural change immediately before and after dosing, and one and five hours after dosing, during the working week. Animals were observed immediately before and after dosing, and one hour after dosing at weekends (except for females during parturition where applicable). During the treatment-free period, animals were observed twice daily, morning and afternoon (once daily at weekends). All observations were recorded.

3.3.2 Functional Observations

Prior to the start of treatment and at weekly intervals thereafter, all non-recovery animals were observed for signs of functional/behavioural toxicity. Functional performance tests were also performed on five selected males and females per dose level, prior to termination, together with an assessment of sensory reactivity to various stimuli.

3.3.2.1 Behavioural Assessments

Detailed individual clinical observations were performed for each non-recovery animal using a purpose-built arena. The following parameters were observed:

Gait	Hyper/Hypothermia
Tremors	Skin colour
Twitches	Respiration
Convulsions	Palpebral closure
Bizarre/Abnormal/Stereotypic behaviour	Urination
Salivation	Defecation
Pilo-erection	Transfer arousal
Exophthalmia	Tail elevation
Lachrymation	

The scoring system used is outlined in Appendix 1.

3.3.2.2 Functional Performance Tests

Motor Activity. Purpose-built 44 infra-red beam automated activity monitors were used to assess motor activity. Animals were randomly allocated to the activity monitors. The tests were performed at approximately the same time each day, under similar laboratory conditions. The evaluation period was thirty minutes for each animal. The time in seconds each animal was active and mobile was recorded for the overall thirty minute period and also during the final 20% of the period (considered to be the asymptotic period).

Forelimb/Hindlimb Grips Strength. An automated grip strength meter was used. Each animal was allowed to grip the proximal metal bar of the meter with its forepaws. The animal was pulled by the base of the tail until its grip was broken. The animal was drawn along the trough of the meter by the tail until its hind paws gripped the distal metal bar. The animal was pulled by the base of the tail until its grip was broken. A record of the force required to break the grip for each animal was made. Three consecutive trials were performed for each animal.

3.3.2.3 Sensory Reactivity

Each animal was individually assessed for sensory reactivity to auditory, visual and proprioceptive stimuli. The scoring system used is outlined in Appendix 1. The following parameters were observed:

Grasp response	Touch escape
Vocalisation	Pupil reflex
Toe pinch	Startle reflex (excluding females)
Tail pinch	Blink reflex
Finger approach	

3.3.3 Bodyweight

Individual bodyweights were recorded on Day 1 (prior to dosing) and then weekly for males until termination. Females were weighed weekly until mating was evident. Bodyweights were then recorded on Days 0, 7, 14 and 20 *post coitum*, and on Days 1 and 4 *post partum*. Recovery animals were weighed on Day 1 and then weekly until termination.

3.3.4 Food Consumption

During the maturation period, weekly food consumption was recorded for each cage of adults. This was continued for males after the mating phase. For females showing evidence of mating, food consumption was recorded for the periods covering Days 0-7, 7-14 and 14-21. For females

with live litters, food consumption was recorded on Days 1 and 4 *post partum.* Food consumption for Recovery animals was recorded weekly until termination.

3.3.5 Water Consumption

Daily visual inspection of water bottles during Week 1 revealed possible intergroup differences. Water consumption was therefore measured and recorded for each cage group from Week 2 onwards.

3.3.6 Laboratory Investigations

Haematological and blood chemical investigations were performed on five non-recovery males and five non-recovery females selected from each test and control group on Day 14 (day prior to pairing). Blood chemical and haematological assessments were performed on five Non-recovery animals at termination and on Recovery animals on Day 57. Blood samples were obtained from the lateral tail vein. Animals were not fasted prior to sampling.

The methods used for haematological and blood chemical investigations are given in Appendix 24.

3.3.6.1 Haematology

The following parameters were measured on blood collected into tubes containing potassium EDTA anti-coagulant:

Haemoglobin (Hb)	
Erythrocyte count (RBC)	
Haematocrit (Hct)	
Erythrocyte indices	- mean corpuscular haemoglobin (MCH)
	- mean corpuscular volume (MCV)
	- mean corpuscular haemoglobin concentration (MCHC)
Total leucocyte count (WBC)	
Differential leucocyte count	- neutrophils (Neut)
	- lymphocytes (Lymph)
	- monocytes (Mono)
	- eosinophils (Eos)
	- basophils (Bas)
Platelet count (PLT)	
Reticulocyte count (Retic)	- Cresyl blue stained slides were prepared but reticulocytes were not assessed

Prothrombin time (CT) was assessed by 'Thrombomax HS with calcium' and Activated partial thromboplastin time (APTT) was assess by 'Actin FS' using samples collected into sodium citrate solution (0.11 mol/l).

3.3.6.2 Blood Chemistry

The following parameters were measured on plasma from blood collected into tubes containing lithium heparin anti-coagulant:

Urea	Calcium (Ca++)
Glucose	Inorganic phosphorus (P)
Total protein (Tot.Prot.)	Aspartate aminotransferase (ASAT)
Albumin	Alanine aminotransferase (ALAT)
Albumin/Globulin (A/G) ratio (by calculation)	Alkaline phosphatase (AP)
Sodium (Na+)	Creatinine (Creat)
Potassium (K+)	Total cholesterol (Chol)
Chloride (Cl^-)	Total bilirubin (Bili)

3.3.6.3 Urinalysis

The following parameters were measured on collected urine:

Volume	Ketones
Specific gravity	Bilirubin
pH	Urobilinogen
Protein	Reducing substances
Glucose	Blood

3.3.7 Reproduction Screening (Non-Recovery Animals)

3.3.7.1 Mating

Animals were paired on a 1 male: 1 female basis within each dose group, for a period of up to fourteen days. Cage tray-liners were checked each morning for the presence of ejected copulation plugs and each female was examined for the presence of a copulation plug in the vagina. A vaginal smear was prepared for each female and the stage of the oestrous cycle or the presence of sperm was recorded. The presence of sperm within the vaginal smear and/or vaginal plug *in situ* was taken as positive evidence of mating and the males were subsequently returned to their original holding cages. Mated females were housed individually during the period of gestation and lactation.

3.3.7.2 Pregnancy and Parturition

Each pregnant female was observed at approximately 0830, 1230 and 1630 hours around the period of expected parturition. Observations were carried out at approximately 0830 and 1230 hours at weekends and public holidays. The following was recorded for each female:

i) Date of mating

jj) Date and time of observed start of parturition

iii) Date and time of observed completion of parturition

3.3.7.3 Litter Data

On completion of parturition, the number of live and dead offspring was recorded.

For each litter the following was recorded:

i) Number of pups born

ii) Number and sex of pups alive recorded daily and reported on Day 1 and 4 *post partum*

iii) Clinical condition of pups from birth to Day 4 *post partum*

iv) Individual pup and litter weights on Day 1 and 4 *post partum*

3.3.7.4 Physical Development

All live offspring were observed for the detachment of pinna and assessed for reflexological response to stimuli by assessing surface righting reflex on Day 1 *post partum.*

3.3.8 Pathology

Non-Recovery adult males were killed by intravenous overdose of sodium pentobarbitone followed by exsanguination on Day 43. Non-recovery adult females were killed by intravenous overdose of sodium pentobarbitone followed by exsanguination on Day 5 *post partum.* Surviving offspring were terminated via intracardiac overdose of sodium pentobarbitone. Recovery animals were killed by intravenous overdose of sodium pentobarbitone followed by exsanguination on Day 57.

In addition, the corpora lutea of all ovaries from pregnant females were counted at necropsy. The uterine implantation sites were counted. The procedure was enhanced by staining the uteri with a 1% ammonium polysulphide solution.

All adult animals and offspring, including those dying during the study, were subjected to a full external and internal examination, and any macroscopic abnormalities were recorded.

3.3.8.1 Organ Weights

The following organs, removed from the five selected non-recovery and recovery adult animals that were killed at the end of the study, were dissected free from fat and weighed before fixation. In addition, the reproductive organs shown in **bold** were weighed from all non-recovery animals:

Adrenals	Liver
Brain	**Ovaries**
Epididymides	Spleen
Heart	**Testes**
Kidneys	Thymus

3.3.8.2 Histopathology

Samples of the following tissues were preserved from five males and five females from each dose group, in buffered 10% formalin. The tissues shown in **bold** were also removed from the remaining animals:

Adrenals	**Ovaries**
Aorta (thoracic)	Pancreas
Bone & bone marrow (femur including stifle joint)	**Pituitary**
Bone & bone marrow (sternum)	**Prostate**
Brain (including cerebrum, cerebellum and pons)	Oesophagus
Caecum	Rectum
Coagulating gland	Salivary glands (submaxillary)
Colon	Sciatic nerve
Duodenum	**Seminal vesicles**
Epididymides *	Skin (hind limb)
Eyes	Spinal cord (cervical)
Gross lesions	Spleen
Heart	Stomach
Ileum	Thyroid/parathyroid
Jejunum	Trachea
Kidneys	**Testes ***

* = preserved in Bouin's fluid and then in 70% IMS after forty-eight hours
* = preserved in Bouins fluid and then in 70% IMS after forty-eight hours

Liver	Thymus
Lungs (with bronchi) #	Urinary bladder
Lymph nodes (cervical and mesenteric)	**Uterus/Cervix**
Mammary gland	**Vagina**
Muscle (skeletal)	

All tissues were despatched to Propath UK Ltd, Willow Court, Netherwood Road, Rotherwas, Hereford, UK (Principle Investigator: N Candy). The tissues from five selected control and 600 mg/kg/day dose group animals were prepared as paraffin blocks, sectioned at nominal thickness of 5mm and stained with haematoxylin and eosin for subsequent microscopic examination. The tissues shown in **bold** from the remaining control and 600 mg/kg/day animals were also processed.

Microscopic examination was conducted by the Study Pathologist. All findings were entered into the ROELEE Pathology computerisation system for tabulation and report production.

3.4 Evaluation of Data

3.4.1 Treatment of Data

Data were processed to give group mean values and standard deviations where appropriate. The values shown in Appendices may be rounded for presentation purposes. Group Mean values are frequently calculated from unrounded values therefore it may not be possible to calculate the exact mean value from the values presented in the Appendices.

Group mean values for bodyweights, bodyweight change and food consumption were calculated using all pregnant/littering females.

Food conversion efficiency was calculated using the formula:

$$\text{Food efficiency} = \frac{\text{Group mean bodyweight gain (g/rat)}}{\text{Group mean food consumption (g/rat/day)}}$$

Food efficiency was not calculated during late gestation/lactation due to foetal growth/milk production.

= lungs were inflated to approximately normal inspiratory volume with buffered 10% formalin before immersion in fixative

3.4.2 Reproductive Indices

3.4.2.1 Mating Performance and Fertility

The following parameters were calculated from the individual data during the mating period of the parental generation.

i) Pre-coital Interval

Calculated as the time elapsing between initial pairing and the observation of positive evidence of mating.

ii) Fertility Indices

For each group the following were calculated:

$$\text{Mating Index (\%)} = \frac{\text{Number of animals mated}}{\text{Number of animals paired}} \text{ x } 100$$

$$\text{Pregnancy Index (\%)} = \frac{\text{Number of pregnant females}}{\text{Number of animals mated}} \text{ x } 100$$

3.4.2.2 Gestation and Parturition Data

The following parameters were calculated for individual data during the gestation and parturition period of the parental generation.

i) Gestation Length

Calculated as the number of days of gestation including the day for observation of mating and the start of parturition.

ii) Parturition Index

The following was calculated for each group:

$$\text{Parturition Index (\%)} = \frac{\text{Number of females delivering live offspring}}{\text{Number of pregnant females}} \text{ x } 100$$

3.4.2.3 Litter Data

The standard unit of assessment was considered to be the litter, therefore values were first calculated for each litter and the group mean was calculated using their individual litter values. Group mean values included all litters reared to termination (Day 5 of age).

i) Implantation Losses (%)

Group mean percentile pre-implantation and post implantation loss were calculated for each female/litter as follows:

$$\%\ \text{pre - implantation loss} = \frac{\text{Number of Corpora Lutea - Number of implantation sites}}{\text{Number of corpora lutea}} \times 100$$

$$\%\ \text{post - implantation loss} = \frac{\text{Number of implantation sites - number of offspring}}{\text{Number of implantation sites}} \times 100$$

ii) Live Birth and Viability Indices

The following indices were calculated for each litter as follows:

$$\text{Live Birth Index (\%)} = \frac{\text{Number of offspring alive on Day 1}}{\text{Number of offspring born}} \times 100$$

$$\text{Viability Index (\%)} = \frac{\text{Number of offspring alive on Day 4}}{\text{Number of offspring alive on Day 1}} \times 100$$

iii) Sex Ratio (% males)

Sex ratio was calculated for each litter value on Day 1 and 4 *post partum*, using the following formula:

$$\frac{\text{Number of male offspring}}{\text{Number of offspring of determined sex}} \times 100$$

3.4.3 Statistical Analysis

Haematological, blood chemical, organ weight (absolute and relative to terminal bodyweight), weekly bodyweight gain, litter weights, offspring bodyweights and quantitative functional performance data were assessed for dose response relationships by linear regression analysis, followed by one way analysis of variance (ANOVA) incorporating Levene's test for homogeneity of variance. Where variances were shown to be homogenous, pairwise comparisons were conducted using Dunnett's test. Where Levene's test showed unequal variances the data were analysed using non-parametric methods: Kruskal-Wallis ANOVA and Mann-Whitney 'U' test.

The non-parametric methods were also used to analyse implantation loss, offspring sex ratio and landmark developmental markers.

The haematology variable basophils was not analysed since consistently greater than 30% of the data were recorded as the same value.

Probability values (p) are presented as follows:

$p < 0.001$ ***
$p < 0.01$ **
$p < 0.05$ *
$p \geq 0.05$ (not significant)

4. ARCHIVES

Unless instructed otherwise by the Sponsor, specimens, all original data (including test site generated data) and the final report will be retained in the Safepharm archives for five years, after which instructions will be sought as to further retention or disposal.

5. RESULTS

ADULT RESPONSES

5.1 Mortality

One control female was killed *in extremis* due to difficulties during parturition. There were no further unscheduled deaths.

5.2 Clinical Observations

A summary incidence of daily clinical observations is given in Table 2 to Table 5.

Animals of either sex treated with 600 mg/kg/day showed increased salivation from Day 1 (males) and Day 5 (females) onwards. Episodes of hunched posture, ataxia, generalised red/brown fur staining, wet fur and orange staining on cage tray liners were evident in animals of either sex treated with 600 mg/kg/day throughout the treatment period. Isolated incidents of lethargy, tiptoe gait and increased lachrymation (females only) were also evident throughout the treatment period at this treatment level.

Animals of either sex treated with 175 mg/kg/day showed increased salivation from Day 7 (males) and Day 13 (females) onwards. Males treated with 175 mg/kg/day also showed orange staining on cage tray liners during the first two weeks of treatment and ataxia on Days 39 and 40.

Males treated with 50 mg/kg/day showed instances of increased salivation from Day 8 onwards and red/brown stained fur on Day 39.

No such toxicologically significant effects were detected in females treated with 50 mg/kg/day.

One female treated with 50 mg/kg/day had noisy respiration on Day 17. In isolation this was considered of no toxicological significance.

5.3 Functional Observations

A summary incidence of behavioural assessments is given in Table 6 and Table 7. Group mean functional test values and standard deviations are given in Table 8 and Table 9. Individual values are given in Appendix 2. A summary incidence of sensory reactivity assessments is given in Table 10 and Table 11. Individual responses are given in Appendix 3.

5.3.1 Behavioural Assessment

Weekly open field arena observations confirmed the clinical signs of increased salivation detected during Week 3, tiptoe gait detected during Week 5 and hunched posture, tiptoe gait and increased salivation detected during Week 6 for males treated with 600 mg/kg/day. Open field assessments also confirmed the clinical signs of ataxia, hunched posture and tiptoe gait detected during Week 1, tiptoe gait detected during Weeks 2 and 5 and increased salivation and tiptoe gait detected during the Day 4 *post partum* assessments for females treated with 600 mg/kg/day.

No such effects were detected in animals of either sex treated with 175 or 50 mg/kg/day.

All remaining inter and intra group differences in urination, defecation and transfer arousal scores were considered to be a result of normal variation for rats of the strain and age used and were of no toxicological importance.

5.3.2 Functional Performance Tests

There were no treatment-related changes in the functional performance parameters measured.

Statistical analysis of the data revealed no significant intergroup differences.

5.3.3 Sensory Reactivity Assessments

There were no treatment-related changes in sensory reactivity.

All inter and intra group differences in sensory reactivity scores were considered to be a result of normal variation for rats of the strain and age used and were of no toxicological importance.

5.4 Bodyweight

Group mean bodyweight and bodyweight change for males are given in Table 12. Group mean bodyweight and bodyweight change for females are given in Table 13. These are presented graphically in Figure 1 and Figure 2. Individual data are given in Appendix 4 and 5.

5.4.1 Maturation Bodyweight

Males treated with 600 mg/kg/day showed a reduction in bodyweight gain during Weeks 1, 2, 4 and 6, with statistical significance being achieved during Weeks 1 and 4. Females treated with 600 mg/kg/day showed a slight reduction in bodyweight gain during Week 2 of maturation, although statistical significance was not achieved.

No adverse effect on bodyweight gain was detected for males treated with 175 or 50 mg/kg/day throughout the treatment period or for females treated with 175 or 50 mg/kg/day throughout the two week maturation period.

5.4.2 Gestation Bodyweight

Bodyweight gains for treated females throughout the gestation phase of the study were comparable to controls.

There were no significant intergroup differences.

5.4.3 Lactation Bodyweights

Bodyweight gains for treated females throughout the lactation phase of the study were comparable to controls.

There were no significant intergroup differences.

5.5 Food Consumption

Group mean food consumptions for males are given in Table 14 and group mean food consumptions during the maturation, gestation and lactation phases for females are given in Table 15. Individual data for gestation and lactation are given in Appendix 6. Group mean food consumptions for recovery females are given in Table 15. These are presented graphically in Figure 3 and Figure 4. Food efficiencies are given in Tables 16 and 17.

5.5.1 Maturation

There were no adverse effects on food consumption for males throughout the study or for females during the two week maturation period.

A slight reduction in food efficiency was detected for males treated with 600 mg/kg/day during Week 6 and for females from this treatment group during Week 2 of maturation.

No such effects in food efficiency were detected in animals of either sex treated with 175 or 50 mg/kg/day.

5.5.2 Gestation

Food consumption for treated females throughout the gestation phase of the study was comparable to controls.

There were no significant intergroup differences.

5.5.3 Lactation

Food consumption for treated females throughout the lactation phase of the study was comparable to controls.

There were no significant intergroup differences.

5.6 Water Consumption

Group mean water consumptions for males are given in Table 18 and group mean water consumptions during the maturation, gestation and lactation phases for females are given in Table 19. Individual data for gestation and lactation are given in Appendix 7. Group mean water consumptions for recovery females are given in Table 19.

5.6.1 Maturation

Daily visual inspection of water bottles revealed overt intergroup differences during the first week of dosing and, as such, measurement of water consumption was initiated during the second week of maturation. Gravimetric measurement revealed an increase in water consumption for males treated with 600 mg/kg/day from Day 8 onwards and for females treated with 600 mg/kg/day during the second week of maturation.

5.6.2 Gestation

Gravimetric measurement of water consumption throughout the gestation phase of the study showed statistically significant increases for females treated with 600 mg/kg/day.

No such effects were detected in females treated with 175 or 50 mg/kg/day.

5.6.3 Lactation

Gravimetric measurement of water consumption throughout the lactation phase of the study did not reveal any significant intergroup differences.

5.7 Laboratory Investigations

5.7.1 Haematology

Group mean values and standard deviations for test and control group animals are given in Table 20 and Table 21 (statistically significant differences are indicated). Individual data are given in Appendix 8.

There were no treatment-related effects in the haematological parameters measured.

There were no significant intergroup differences.

5.7.2 Blood Chemistry

Group mean values and standard deviations for test and control group animals are given in Table 22 and Table 23 (statistically significant differences are indicated). Individual data are given in Appendix 9.

There were no treatment-related effects in the blood chemical parameters measured.

During the pre-mating assessment females from all treatment groups and males treated with 600 and 175 mg/kg/day showed statistically significant increases in albumin. Animals of either sex treated with 600 mg/kg/day and males treated with 175 mg/kg/day also showed an increase in total protein. By termination, albumin and total protein levels were no longer significantly different from controls and the earlier differences were therefore considered to be of no long term toxicological significance. Statistically significant reductions in plasma urea and chloride concentration were detected in females treated with 600 and 175 mg/kg/day during the pre-mating assessment. Females treated with 600 mg/kg/day also showed reductions in plasma glucose and sodium concentration. Males treated with 600 and 175 mg/kg/day showed statistically significant increases in creatinine levels during the pre-mating assessment with males treated with 175 mg/kg/day also showing a reduction in chloride concentration and an increase in potassium concentration during the terminal assessments. In the absence of any histopathological correlates to suggest an adverse renal effect; the intergroup differences were considered of no toxicological importance.

5.7.3 Urinalysis

Group mean values and standard deviations, for test and control group males are given in Table 24. Individual data are given in Appendix 10.

There were no treatment-related changes in the urinalytical parameters measured.

There were no significant intergroup differences.

5.8 Reproductive Performance

5.8.1 Mating Performance and Fertility

Group mean mating performance and summary incidence of pre-coital intervals are presented in Table 25. Individual values are given in Appendix 11.

There were no treatment-related effects on mating performance or fertility. The distribution of pre-coital intervals for treated animals was comparable to controls; with the majority of animals showing positive evidence of mating within four days of pairing. Only one 50 mg/kg/day female failed to achieve pregnancy.

5.8.2 Gestation

A summary incidence of gestation length and parturition indices is presented in Table 26. Individual values are given in Appendix 11.

There were no significant intergroup differences in gestation lengths or parturition indices. The distribution for treated females was comparable to controls.

LITTER RESPONSES

In total there were 9, 9, 10 and 10 females at 0 (control), 50, 175 and 600 mg/kg/day respectively who gave birth to a live litter and successfully reared young to Day 5 of age and have been included in the following assessment of litter responses.

5.8.3 Litter Size and Viability

Group mean litter size, live birth and viability indices and sex ratio are presented in Tables 27, 28 and 29. Individual values are shown in Appendices 12, 13 and 14.

The mean numbers of corpora lutea observed for treated females did not indicate any adverse effect of treatment at 50, 175 or 600 mg/kg/day. Subsequent pre-natal losses and resultant litter

size at Day 1 for treated animals were similar to controls. Post-natal survival was unaffected in all treated groups with litter size at Day 4 again being similar to controls.

5.8.4 Offspring Growth and Development

Group mean litter weights and pup weights are given in Table 27. Individual values are presented in Appendix 12. Group mean refelxological responses are presented in Table 31. Individual data is shown in Appendix 16.

Mean offspring bodyweight and subsequent mean litter weights were reduced on Day 1 and 4 *post partum* for litters treated with 600 mg/kg/day. A statistically significant reduction in mean offspring bodyweight gain was also detected for these litters between Days 1 and 4 *post partum*.

No such effects were detected for litters treated with 175 or 50 mg/kg/day. Inter-group differences in offspring maturation and reflexological assessment (percentage successful at surface righting) did not indicate any adverse effects of treatment at 50, 175 or 600 mg/kg/day.

5.8.5 Clinical signs of Offspring

A summary incidence of daily clinical observations is given in Table 30. Individual observations are presented in Appendix 15.

No toxicologically significant clinical findings were observed. The type and incidence of clinical observations recorded for offspring throughout the dose groups were consistent with what is normally expected of the age examined and were of no toxicological importance.

5.9 Pathology

5.9.1 Offspring Necropsy Findings

A summary incidence of necropsy findings is presented in Table 32 and individual findings are given in Appendix 17.

The macroscopic findings observed for interim deaths and terminal kill offspring throughout the treatment groups, were consistent with normally expected low incidence findings in offspring of the age examined and were of no toxicological importance.

5.9.2 Adult Necropsy

A summary incidence of necropsy findings is given in Tables 33 and 34. Individual data are given in Appendix 18.

No treatment-related macroscopic abnormalities were detected at terminal kill.

The control female killed *in extremis* during parturition had pale adrenals and fifteen foetuses in the uterus and two foetuses with placentas positioned close to the bifurcation of the uterine horns.

One male treated with 600 mg/kg/day showed a red fluid filled bladder. A further male from this treatment group showed a small left testis and epididymis at necropsy. In the absence of any histopathological correlates, these findings were considered to be of no toxicological significance. Hydronephrosis of the kidneys was confined to one male treated with 175 mg/kg/day. This is a low incidence congenital abnormality and is unrelated to test material toxicity. One terminal kill female treated with 175 mg/kg/day showed gaseous distension of the intestines. In the absence of a similar effect in high dose animals the intergroup difference was considered of no toxicological importance.

5.9.3 Organ Weights

Group mean absolute and relative organ weights and standard deviations for test and control group adult animals are presented in Tables 35 to 39. Individual data are given in Appendix 19.

Females treated with 600 mg/kg/day showed a statistically significant increase in liver weight, both absolute and relative to terminal bodyweight. The increased relative liver weight effect continued into recovery 600 mg/kg/day females following fourteen days without treatment.

No toxicologically significant effects were detected in males treated with 600 mg/kg/day, animals of either sex treated with 175 or 50 mg/kg/day or recovery males following fourteen days without treatment.

Non-recovery and recovery males treated with 600 mg/kg/day showed an increase in relative liver weight. In the absence of any histological correlates the intergroup differences were considered of no toxicological significance. Recovery males treated with 600 mg/kg/day also showed a reduction in absolute spleen weight. In the absence of a similar effect seen in non-recovery males or any histological correlates the intergroup difference was considered of no toxicological importance. Females treated with 175 mg/kg/day showed an increase in absolute liver weight. In the absence of a dose-related response the intergroup difference was considered to be of no toxicological significance.

5.9.4 Histopathology

A summary incidence of histopathological findings is given in Table 39 and Table 40. All individual data are given in Appendix 20.

The following treatment-related microscopic findings were detected:

LIVER: Centrilobular hepatocyte enlargement was observed in relation to treatment for females treated with 600 mg/kg/day but not at any other dose level. Males were not similarly affected. Only three animals were affected to a minimal severity and this was considered to be a marginal response to treatment.

Hepatocyte enlargement is commonly observed in the rodent liver following the administration of xenobiotics and, in the absence of associated inflammatory or degenerative changes, is generally considered to be adaptive in nature. A single instance of centrilobular hypertrophy was seen among Recovery 600 mg/kg/day females indicating regression of the condition following an additional fourteen days without treatment.

THYROID: Follicular cell hypertrophy was observed as an effect of treatment for females treated with 600 mg/kg/day but probably not at any other treatment level. Males were not similarly affected, the group distribution of the lesion being more variable.

Follicular cell hypertrophy occurs spontaneously among control rats and there was considered to be a marginal effect of treatment for high dose level females in this investigation. The condition was observed to have regressed among Recovery 600 mg/kg/day females after completion of the fourteen day recovery period.

OESOPHAGUS: A higher incidence of mononuclear cell infiltration in the peripheral musculature was observed among females treated with 600 and 175 mg/kg/day.

Such change commonly results from the physical trauma of gavage dosing and is frequently seen among control animals although such was not the case in this study. The possibility that this is a consequence of test material administration cannot be excluded although the mechanism by which it occurred is not immediately apparent.

6. DISCUSSION

The oral administration of 1,5-Cyclooctadiene (COD) to rats for a period of up to forty two days at dose levels of up to 600 mg/kg/day resulted in treatment-related systemic changes in animals of either sex treated with 600 mg/kg/day, and in females treated with 175 mg/kg/day.

Clinical signs were evident in animals of either sex treated with 600 mg/kg/day. Increased salivation and episodes of hunched posture, ataxia, generalised red/brown fur staining, wet fur and orange staining on cage tray liners were evident throughout the treatment period. Isolated instances of lethargy, tiptoe gait and increased lachrymation (females only) were also evident. Several of these observations were also supported behaviourally following weekly open field assessments. Increased salivation and orange staining on cage tray liners were also evident in animals of either sex treated with 175 mg/kg/day. Slight reductions in bodyweight gains were evident for 600 mg/kg/day males during Weeks 1, 2, 4 and 6 of the study. Reduced bodyweight gain was also observed for females treated at the highest dose level during the second week of maturation. Food efficiency was reduced during Week 2 for females and Week 6 for males at 600 mg/kg/day. Water consumptions were also adversely affected in these animals from Day 8 of maturation onwards and throughout gestation and lactation.

Liver weight was elevated in females at 600 mg/kg/day and microscopic examination of liver sections revealed changes identified as centrilobular hepatocyte enlargement. In the absence of associated inflammatory or degenerative changes this condition is however, almost certainly adaptive in nature. The condition did regress in recovery 600 mg/kg/day females following fourteen days without treatment, however relative liver weight still remained slightly elevated.

Microscopic changes were also identified in the thyroids. Follicular cell hypertrophy was observed for females treated with 600 mg/kg/day. Thyroxine is ultimately excreted via the bile, having first been conjugated in the liver. It is conceivable that conjugating hepatic enzymes may have been induced as a response to the test material therefore increasing thyroxine excretion and stimulating thyroxine stimulating hormone and thyroxine production resulting in the microscopic changes identified. Histopathological changes were identified in the oesophagus as higher incidence of mononuclear cell infiltration in the peripheral musculature of females treated with 600 and 175 mg/kg/day. Such changes are a common result from the physical trauma of gavage dosing and are frequently seen among control animals, although such was not the case in this study. The possibility that this is a consequence of test material administration however cannot be entirely excluded, although the mechanism by which it occurred is not immediately apparent.

Mean offspring bodyweight and subsequent mean litter weights were reduced on Day 1 and 4 *post partum* for litters treated with 600 mg/kg/day. A statistically significant reduction in mean offspring bodyweight gain was also detected for these litters between Days 1 and 4 *post partum*.

7. CONCLUSION

The oral administration of 1,5-Cyclooctadiene (COD) to rats by gavage at dose level of 600, 175 and 50 mg/kg/day resulted in treatment-related changes in males treated with 600 mg/kg/day and in females treated with 600 and 175 mg/kg/day. The 'No Observed Effect Level' (NOEL) was therefore considered to be 175 mg/kg/day for males and 50 mg/kg/day for females.

Slight bodyweight reductions and increased water consumptions detected in animals of either sex treated with 600 mg/kg/day were considered not to represent "serious damage" to health as defined by the criteria given in the EC labelling guide of Commission Directives 2004/9/EC and 2004/10/EC. The microscopic changes observed in females at 600 and 175 mg/kg/day were regarded as adaptive in nature or as a common result from the physical trauma of gavage dosing. The "No Observed Adverse Effect Level" (NOAEL) for either sex was therefore considered to be 600 mg/kg/day.

Treatment-related effects on reproduction were observed as a reduced offspring bodyweight and subsequent mean litter weights on Days 1 and 4 *post partum* for female litters treated with 600 mg/kg/day together with a reduction in mean bodyweight gain between Days 1 and 4 *post partum*. No such effects were detected at 175 or 50 mg/kg/day, therefore the "No Observed Effect Level" (NOEL) for reproductive toxicity was considered to be 175 mg/kg/day.

1,5-CYCLOOCTADIENE (COD): ORAL GAVAGE COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING IN THE RAT

TABULAR SUMMARY REPORT OF EFFECTS ON REPRODUCTION/DEVELOPMENT

Observations			Dose Level (mg/kg/day)			
			0 (Control)	50	175	600
Mated pairs		*n*	10	10	10	10
Females showing evidence of copulation		*n*	10	10	10	10
Pregnant females		*n*	10	9	10	10
Conception Days 1-4		*n*	10	9	10	10
Gestation = 22 days		*n*	5	3	2	1
Gestation = 22½ days		*n*	1	2	4	3
Gestation = 23 days		*n*	4	4	4	6
Dams with live young born		*n*	9	9	10	10
Dams with live young at Day 4 *post partum*		*n*	9	9	10	10
Corpora lutea/dam		$\bar{x}$	16.4	16.4	17.0	17.8
Implants/dam		$\bar{x}$	14.0	15.8	15.4	15.0
Live offspring/dam Day 1 *post partum*		$\bar{x}$	13.2	14.1	14.1	13.2
Live offspring/dam at Day 4 *post partum*		$\bar{x}$	13.0	14.1	14.1	13.0
Sex ratio: % males at Birth		$\bar{x}$	54.7	47.6	46.4	44.1
Sex ratio: % males Day 1 *post partum*		$\bar{x}$	54.1	47.9	46.4	44.1
Sex ratio: % males at Day 4 *post partum*		$\bar{x}$	54.1	47.9	46.4	43.2
Litter weight (g) at Day 1 *post partum*		$\bar{x}$	93.1	97.9	98.5	82.9
Litter weight (g) at Day 4 *post partum*		$\bar{x}$	135.8	146.3	149.5	115.7
Offspring weight (g) at Day 1 *post partum*	Males	$\bar{x}$	7.3	7.1	7.2	6.5
	Females	$\bar{x}$	6.9	6.8	6.8	6.2
Offspring weight (g) at Day 4 *post partum*	Males	$\bar{x}$	10.8	10.5	10.7	9.2
	Females	$\bar{x}$	10.4	10.2	10.2	8.8
LOSS OF OFFSPRING/DAM						
Pre-implantation (corpora lutea minus implantations)						
0		*n*	1	3	4	2
1		*n*	1	2	2	2
2		*n*	2	1	2	1
3		*n*	2	2	0	2
4		*n*	1	0	0	1
5		*n*	1	0	2	0
7		*n*	0	0	0	2
Pre-natal (implantations minus live births)						
0		*n*	5	3	2	2
1		*n*	2*	3	5	4
2		*n*	0	2	3	3
3		*n*	1	0	0	1
Post natal (live births minus offspring alive on Day 4 *post partum*)						
0		*n*	5	5	8	6
1		*n*	2	4	2	2
2		*n*	2	0	0	1
4		*n*	0	0	0	1

n = Number
$\bar{x}$ = Mean
* = data unavailable for two females

TABLES

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 1 Summary of Reproductive Performance

	Dose Group (mg/kg/day)			
	0 (Control)	50	175	600
Males				
Initial Group Size	10	10	10	10
Paired	10	10	10	10
Induced pregnacy in female partner	10	9	10	10
Surived to terminal necropsy	10	10	10	10
Females				
Initial Group Size	10	10	10	10
Paired	10	10	10	10
Non-pregnant	0	1	0	0
Animal killed *in extremis* during littering	1	0	0	0
Reared young to Day 5 *post partum*	9	9	10	10

Table 2 Clinical Observations for Males - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 1			Day: 2			Day: 3			Day: 4			Day: 5			Day: 6			Day: 7		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
175♦▲	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
600■●	10	Hunched posture	0	4	0	0	0	0	0	0	2	0	0	*	0	0	*	0	0	1	0	0	0
		Increased salivation	0	1	1	0	0	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		Lethargy	0	1	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		Tiptoe gait	0	1	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		Wet fur	0	0	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	0	0	1	1
		No abnormalities detected	10	5	9	10	10	10	10	10	8	10	10	*	10	10	*	10	10	9	10	9	9

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing between Day 2 and 7 inclusive
♦ = increased salivation detected up to ten minutes after dosing on Day 7 only
● = orange staining on cage tray liners between Days 5 and 7.
▲ = orange staining on cage tray liners between Days 6 and 7 inclusive.

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 2 (continued) Clinical Observations for Males - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 8			Day: 9			Day: 10			Day: 11			Day: 12			Day: 13			Day: 14		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	*	10	10	10
50†	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	*	10	10	10
175♦●	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	*	10	10	10
600■●	10	Hunched posture	0	0	0	0	2	0	0	0	0	0	0	*	0	0	*	0	0	*	0	0	0
		Increased salivation	0	2	0	0	1	0	0	0	1	1	4	*	1	0	*	1	3	*	1	1	0
		Red/brown stained fur	1	1	1	1	1	1	0	0	2	2	2	*	2	2	*	2	2	*	0	0	0
		Wet fur	0	0	0	0	0	0	0	0	0	0	1	*	0	0	*	0	3	*	0	0	0
		No abnormalities detected	9	7	9	9	7	9	10	10	8	8	4	*	8	8	*	8	4	*	9	9	10

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend or on a public holiday
† = increased salivation detected up to ten minutes after dosing on Day 8 only
■ = increased salivation detected up to ten minutes after dosing between Day 8 and 14 inclusive
♦ = increased salivation detected up to ten minutes after dosing between Days 8 and 14
● = orange staining on cage tray liners between Days 8 and 14 inclusive

Table 2 (continued) **Clinical Observations for Males - Group Incidences**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																			
			Day: 15			Day: 16			Day: 17			Day: 18			Day: 19			Day: 20			Day: 21		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
175♦	10	Increased salivation	0	0	0	0	0	0	0	0	1	0	0	*	0	1	*	0	2	0	0	2	0
		No abnormalities detected	10	10	10	10	10	10	10	10	9	10	10	*	10	9	*	10	8	10	10	8	10
600■	10	Ataxia	0	0	0	0	0	0	0	1	0	0	3	*	0	1	*	0	2	0	0	0	0
		Increased salivation	0	4	4	0	8	1	1	1	1	0	3	*	2	2	*	1	2	2	4	6	0
		No abnormalities detected	10	6	6	10	2	9	9	9	9	10	6	*	8	7	*	9	7	8	6	4	10

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing between Days 15 and 21 inclusive
♦ = increased salivation detected up to ten minutes after dosing between Day 18 and 21 inclusive

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 2 (continued) Clinical Observations for Males - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 22			Day: 23			Day: 24			Day: 25			Day: 26			Day: 27			Day: 28		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
50†	10	Wound on neck	0	0	0	0	0	0	0	0	0	1	1	*	1	1	*	0	0	0	0	0	0
		No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
175 ■	10	Increased salivation	0	5	0	0	0	0	0	0	0	0	0	*	0	3	*	0	3	0	0	2	0
		No abnormalities detected	10	5	10	10	10	10	10	10	10	10	10	*	10	7	*	10	7	10	10	8	10
600 ■ ●	10	Ataxia	0	0	0	0	0	0	0	1	0	0	2	*	0	2	*	0	0	0	0	0	0
		Hunched posture	0	0	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	0	1	0	0
		Increased salivation	0	6	2	2	3	0	1	0	0	1	1	*	2	8	*	3	6	1	1	6	1
		Red/brown staining around mouth	0	0	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	1	0	0	0
		Wet fur	0	0	1	0	3	0	0	3	0	0	0	*	0	0	*	0	0	0	0	1	0
		No abnormalities detected	10	4	7	8	4	10	9	7	10	9	7	*	8	2	*	7	4	8	8	4	9

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
† = increased salivation detected up to ten minutes after dosing on Day 24 only
■ = increased salivation detected up to ten minutes after dosing between Days 22 and 28 inclusive
● = orange staining on cage tray liners on Day 27 only

Table 2 (continued) **Clinical Observations for Males - Group Incidences**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 29			Day: 30			Day: 31			Day: 32			Day: 33			Day: 34			Day: 35		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
175 ■	10	Increased salivation	0	0	0	0	3	0	0	6	0	0	2	*	0	1	*	1	2	1	0	1	0
		No abnormalities detected	10	10	10	10	7	10	10	4	10	10	8	*	10	9	*	9	8	9	10	9	10
600 ● ■	10	Increased salivation	1	5	2	1	4	3	2	10	0	1	4	*	4	7	*	2	10	3	2	10	0
		Wet fur	0	1	0	0	1	0	0	1	0	0	2	*	0	1	*	0	1	0	0	1	0
		No abnormalities detected	9	4	8	9	5	7	8	0	10	9	4	*	6	3	*	8	0	7	8	0	10

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing between Days 29 and 35 inclusive
● = orange staining on cage tray liners on Day 29 only

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 2 (continued) Clinical Observations for Males - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																			
			Day: 36			Day: 37			Day: 38			Day: 39			Day: 40			Day: 41			Day: 42		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
50 †	10	Red/brown staining around snout	0	0	0	0	0	0	0	0	0	0	1	*	0	0	*	0	0	0	0	0	0
		No abnormalities detected	10	10	10	10	10	10	10	10	10	10	9	*	10	10	*	10	10	10	10	10	10
175■	10	Ataxia up to ten minutes after dosing	0	0	0	0	0	0	0	0	0	1	0	*	1	0	*	0	0	0	0	0	0
		Ataxia	0	0	0	0	0	0	0	0	0	0	1	*	0	0	*	0	0	0	0	0	0
		Increased salivation	0	2	0	0	0	0	1	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		No abnormalities detected	10	8	10	10	10	10	9	10	10	10	9	*	10	10	*	10	10	10	10	10	10
600 ■	10	Ataxia	0	0	0	0	0	0	0	0	0	0	0	*	0	0	*	0	2	0	0	2	0
		Increased salivation	4	10	0	4	2	1	1	5	0	0	1	*	1	0	*	0	0	0	1	0	0
		Wet fur up to ten minutes after dosing	0	0	0	0	0	0	0	0	0	3	0	*	5	0	*	3	0	0	1	0	0
		Wet fur	0	3	0	0	3	0	0	2	0	0	0	*	1	1	*	0	3	0	0	1	0
		No abnormalities detected	6	0	10	6	7	9	9	5	10	10	9	*	9	9	*	10	6	10	10	8	10

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
† = increased salivation detected up to ten minutes after dosing between Day 38 and 42 inclusive
■ = increased salivation detected up to ten minutes after dosing – Day 36 to 42 inclusive

Table 3 Clinical Observations for Females - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 1			Day: 2			Day: 3			Day: 4			Day: 5			Day: 6			Day: 7		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	*	10	10	10
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	*	10	10	10
175	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	*	10	10	10
600 ■ ●	10	Ataxia	0	3	0	0	3	0	0	2	1	0	0	*	0	2	*	0	0	0	0	0	0
		Hunched posture	0	7	6	0	0	1	0	2	7	0	0	*	0	0	*	0	0	3	0	0	0
		Increased lacrymation	0	1	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		Lethargy	0	0	0	0	3	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		Red/brown staining around eyes	0	0	1	0	0	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		Tiptoe gait	0	3	3	0	0	0	0	2	4	0	0	*	0	0	*	0	0	0	0	0	0
		No abnormalities detected	10	3	3	10	7	9	10	6	3	10	10	*	10	8	*	10	10	7	10	10	10

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing – Days 5 to 7 inclusive
● = orange staining on cage tray liners – Days 5 to 7 inclusive

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 3 (continued) Clinical Observations for Females - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 8			Day: 9			Day: 10			Day: 11			Day: 12			Day: 13			Day: 14		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	*	10	10	10
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	*	10	10	10
175 ♦	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	*	10	10	10
600 ■ ●	10	Ataxia	0	0	0	0	2	0	0	0	0	0	0	*	0	0	*	0	0	*	0	0	0
		Hunched posture	0	4	0	0	2	0	0	0	0	0	0	*	0	0	*	0	0	*	0	0	0
		Increased salivation	0	0	0	0	0	0	0	0	0	0	1	*	0	0	*	0	1	*	0	0	0
		Tiptoe gait	0	0	0	0	2	0	0	0	0	0	0	*	0	0	*	0	0	*	0	0	0
		Wet fur	0	3	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	*	0	0	0
		No abnormalities detected	10	6	10	10	6	10	10	10	10	10	9	*	10	10	*	10	9	*	10	10	10

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend or on a public holiday
■ = increased salivation detected up to ten minutes after dosing – Days 8 to 14 inclusive
♦ = increased salivation detected up to ten minutes after dosing – Day 13 only
● = orange staining on cage tray liners – Days 8 to 14 inclusive

Table 3 (continued) **Clinical Observations for Females - Group Incidences**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																			
			Day: 15			Day: 16			Day: 17			Day: 18			Day: 19			Day: 20			Day: 21		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
50	10	No abnormalities detected	10	10	10	10	10	10	9	9	10	10	10	*	10	10	*	10	10	10	10	10	10
		Noisy respiration	0	0	0	0	0	0	1	1	0	0	0	*	0	0	*	0	0	0	0	0	0
175 ♦	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
600 ■	10	Ataxia	0	0	0	0	0	0	0	1	0	0	3	*	0	2	*	0	3	0	0	1	1
		Hunched posture	0	0	0	0	0	0	0	0	1	0	0	*	0	0	*	0	0	0	0	0	0
		Increased salivation	0	1	1	0	7	1	1	0	0	0	1	*	0	0	*	1	1	2	0	2	0
		Red/brown staining around mouth	0	0	0	0	0	1	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		Wet fur	0	0	0	0	0	0	0	0	1	0	0	*	0	0	*	0	0	0	0	0	0
		No abnormalities detected	10	9	9	10	3	8	9	9	8	10	7	*	10	8	*	9	7	8	10	7	9

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
♦ = increased salivation detected up to ten minutes after dosing - Day 18 only
■ = increased salivation detected up to ten minutes after dosing – Day 15 to 21 inclusive

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 3 (continued) Clinical Observations for Females - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																			
			Day: 22			Day: 23			Day: 24			Day: 25			Day: 26			Day: 27			Day: 28		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	Generalised fur loss	0	0	0	0	0	0	0	0	0	0	1	*	1	1	*	1	1	1	1	1	1
		No abnormalities detected	10	10	10	10	10	10	10	10	10	10	9	*	9	9	*	9	9	9	9	9	9
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
175 ♦	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
600 ■	10	Ataxia	0	0	0	0	0	0	0	0	0	0	0	*	0	1	*	0	1	0	0	1	0
		Increased salivation	0	6	0	0	1	0	0	0	0	0	0	*	0	1	*	2	2	0	0	5	0
		No abnormalities detected	10	4	10	10	9	10	10	10	10	10	10	*	10	8	*	8	8	10	10	5	10

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
♦= increased salivation detected up to ten minutes after dosing – Days 24 to 28 inclusive
■ = increased salivation detected up to ten minutes after dosing – Day 22 to 28 inclusive

Table 3 (continued) **Summary Incidence of Daily Clinical Observations - Females**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 29			Day: 30			Day: 31			Day: 32			Day: 33			Day: 34			Day: 35		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10	Generalised fur loss	1	1	1	1	1	1	1	1	1	1	1	*	1	1	*	1	1	1	1	1	1
		No abnormalities detected	9	9	9	9	9	9	9	9	9	9	9	*	9	9	*	9	9	9	9	9	9
50	10	No abnormalities detected	10	10	10	10	10	10	10	10	10	10	10	*	10	10	*	10	10	10	10	10	10
175 ♦	10	Increased salivation	0	0	0	0	0	0	0	4	0	0	0	*	0	0	*	0	0	0	0	0	0
		No abnormalities detected	10	10	10	10	10	10	10	6	10	10	10	*	10	10	*	10	10	10	10	10	10
600 ■	10	Increased salivation	0	0	0	0	0	0	0	2	0	0	0	*	0	0	*	0	5	0	0	5	0
		No abnormalities detected	10	10	10	10	10	10	10	8	10	10	10	*	10	10	*	10	5	10	10	5	10

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
♦ = increased salivation detected up to ten minutes after dosing – Day 29 to 32 inclusive
■ = increased salivation detected up to ten minutes after dosing - Day 29 to 35 inclusive

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 3 (continued) Clinical Observations for Females - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																			
			Day: 36			Day: 37			Day: 38			Day: 39			Day: 40			Day: 41			Day: 42		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	10/9	Generalised fur loss	1	1	1	1	1	0	1	0	0	0	0	*	0	0	*	0	0	0	1	1	1
		Hunched posture	0	0	0	0	0	0	1	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		Pallour of extremities	0	0	0	0	0	0	1	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		Pilo-erection	0	0	0	0	0	0	1	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		Littering ◊	0	0	0	0	0	1	3	6	6	2	2	*	1	1	*	0	1	1	0	0	0
		Death	0	0	0	0	0	0	1#	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		No abnormalities detected	9	9	9	9	9	9	5	3	3	7	7	*	8	8	*	9	8	8	8	8	8
50	10	Littering ◊	0	0	0	0	0	1	4	7	7	0	0	*	1	1	*	0	1	1	0	0	0
		No abnormalities detected	10	10	10	10	10	9	6	3	3	10	10	*	9	9	*	10	9	9	10	10	10
175 ♦	10	Littering ◊	0	0	0	0	0	1	1	4	3	5	5	*	2	2	*	1	1	1	0	0	0
		No abnormalities detected	10	10	10	10	10	9	9	6	7	5	5	*	8	8	*	9	9	9	10	10	10
600 ■	10	Ataxia up to ten minutes after dosing	0	0	0	0	0	0	0	0	0	1	0	*	0	0	*	0	0	0	0	0	0
		Ataxia	0	0	0	0	0	0	0	0	0	0	1	*	0	0	*	0	0	0	0	0	0
		Increased salivation	0	3	0	0	0	1	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		Lethargy up to ten minutes after dosing	0	0	0	0	0	0	0	0	0	1	0	*	0	0	*	0	0	0	0	0	0
		Littering ◊	0	0	0	0	0	0	1	1	1	4	4	*	3	3	*	1	1	2	0	1	1
		No abnormalities detected	10	7	10	10	10	9	9	9	9	6	5	*	7	7	*	9	9	8	10	9	9

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
◊ = Animals not dosed and clinical observations not performed during littering
♦ = Increased salivation detected up to ten minutes after dosing – between Days 37 and 42
■ = increased salivation detected up to ten minutes after dosing – Days 36 to 42 inclusive
= animal killed *in extremis*

Table 3 (continued) **Clinical Observations for Females - Group Incidences**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																	
			Day: 43			Day: 44			Day: 45			Day: 46			Day : 47					
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h			
0 (Control)	10/0	Day 5 *post partum* – animal removed for necropsy	5	0	0	2	0	0	1	0	0	1		*						
		No abnormalities detected	4	4	4	2	2	2	1	1	1	0		*						
50	10/0	Day 5 *post partum* – animal removed for necropsy	8	0	0	0	0	0	1	0	0	1		*						
		No abnormalities detected	2	2	2	2	2	2	1	1	1	0		*						
175 ♦	10/0	Day 5 *post partum* – animal removed for necropsy	4	0	0	3	0	0	2	0	0	1		*						
		No abnormalities detected	6	6	6	3	3	3	1	1	1	0		*						
600 ■	10/0	Increased salivation	0	1	0	0	0	0	0	1	0	0	0	*						
		Day 5 *post partum* – animal removed for necropsy	1	0	0	4	0	0	3	0	0	1	0	*	1					
		No abnormalities detected	9	8	8	5	5	5	2	1	2	1	1	*	0					

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
♦ = increased salivation detected up to ten minutes after dosing - Day 43 only
■ = increased salivation detected up to ten minutes after dosing - Days 43 to 46 inclusive

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 4 Clinical Observations for Recovery Males - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																			
			Day: 1			Day: 2			Day: 3			Day: 4			Day: 5			Day: 6			Day: 7		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	5	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	5	5	5	5
600 ■ ▲	5	Ataxia	0	0	0	0	1	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		Hunched posture	0	2	0	0	0	1	0	1	0	0	0	*	0	0	*	0	0	0	0	0	0
		Increased salivation	0	2	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		No abnormalities detected	5	2	5	5	4	4	5	4	5	5	5	*	5	5	*	5	5	5	5	5	5

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing - Days 2 and 3
▲ = orange staining on cage tray liners – Days 5 to 7 inclusive

Table 4 (continued) **Clinical Observations for Recovery Males - Group Incidences**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 8			Day: 9			Day: 10			Day: 11			Day: 12			Day: 13			Day: 14		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	5	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	*	5	5	5
600 ■ ▲	5	Hunched posture	0	1	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	*	0	0	0
		Increased salivation	0	0	0	0	1	0	1	0	0	0	0	*	0	0	*	1	1	*	2	1	0
		No abnormalities detected	5	4	5	5	4	5	4	5	5	5	5	*	5	5	*	4	4	*	3	4	5

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend or on a public holiday
■ = increased salivation detected up to ten minutes after dosing – between Days 8 to 14
▲ = orange staining on cage tray liners - Days 8 to 14 inclusive

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 4 (continued) Clinical Observations for Recovery Males - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																			
			Day: 15			Day: 16			Day: 17			Day: 18			Day: 19			Day: 20			Day: 21		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	5	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	5	5	5	5
600 ■	5	Ataxia	0	0	0	0	0	0	0	0	0	0	0	*	0	1	*	0	5	0	0	0	0
		Increased salivation	0	1	1	0	4	0	0	1	0	0	2	*	0	0	*	0	0	0	3	3	0
		No abnormalities detected	5	4	4	5	1	5	5	4	5	5	3	*	5	4	*	5	0	5	2	2	5

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing – Day 15 to 21 inclusive

Table 4 (continued) **Clinical Observations for Recovery Males - Group Incidences**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 22			Day: 23			Day: 24			Day: 25			Day: 26			Day: 27			Day: 28		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	5	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	5	5	5	5
600 ■	5	Ataxia	0	0	0	0	0	0	0	0	0	0	0	*	0	2	*	0	2	0	0	2	0
		Increased salivation	0	1	1	0	0	0	0	0	0	0	0	*	0	4	*	0	0	0	0	0	0
		No abnormalities detected	5	4	4	5	5	5	5	5	5	5	5	*	5	1	*	5	3	5	5	3	5

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing – Days 22 to 28 inclusive

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 4 (continued) Clinical Observations for Recovery Males - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																			
			Day: 29			Day: 30			Day: 31			Day: 32			Day: 33			Day: 34			Day: 35		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	5	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	5	5	5	5
600 ■ ▲	5	Increased salivation	1	1	1	0	1	0	1	2	0	0	1	*	0	2	*	0	3	2	0	2	0
		No abnormalities detected	4	4	4	5	4	5	4	3	5	5	4	*	5	3	*	5	2	3	5	3	5

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing - Days 29 to 35 inclusive
▲ = orange staining on cage tray liners - Day 29 only

Table 4 (continued) **Clinical Observations for Recovery Males - Group Incidences**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																			
			Day: 36			Day: 37			Day: 38			Day: 39			Day: 40			Day: 41			Day: 42		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	5	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	5	5	5	5
600 ■ ▲	5	Increased salivation	0	5	0	0	2	2	0	2	0	0	0	*	0	0	*	0	0	0	0	0	0
		Wet fur detected up to ten minutes after dosing	0	0	0	0	0	0	0	0	0	0	0	*	1	0	*	1	0	0	0	0	0
		Wet fur	0	0	0	0	0	0	0	0	0	0	0	*	0	0	*	0	1	0	0	0	0
		No abnormalities detected	5	0	5	5	3	3	5	3	5	5	5	*	5	5	*	5	4	5	5	5	5

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing – Days 36 to 42 inclusive
▲ = orange staining on cage tray liners - Days 38 and 41

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 4 (continued) Clinical Observations for Recovery Males - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation											
			Day: 43		Day: 44		Day: 45		Day: 46		Day: 47		Day: 48		Day: 49	
			AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
0 (Control)	5	No abnormalities detected	-	5	5	5	5	5	5	*	5	*	5	5	5	5
600	5	No abnormalities detected	-	5	5	5	5	5	5	*	5	*	5	5	5	5

- = observations not performed in error
* = observations not performed at weekend

Table 4 (continued) **Clinical Observations for Recovery Males - Group Incidences**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation													
			Day: 50		Day: 51		Day: 52		Day: 53		Day: 54		Day: 55		Day: 56	
			AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
0 (Control)	5	No abnormalities detected	5	5	-	5	5	5	5	*	5	*	5	5	5	5
600	5	No abnormalities detected	5	5	-	5	5	5	5	*	5	*	5	5	5	5

- = observations not performed in error
* = observations not performed at weekend

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 5 Clinical Observations for Recovery Females - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 1			Day: 2			Day: 3			Day: 4			Day: 5			Day: 6			Day: 7		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	5	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	5	5	5	5
600 ■ ▲	5	Ataxia	0	1	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	1	0	0	0
		Hunched posture	0	5	2	0	0	0	0	2	3	0	0	*	0	2	*	0	0	3	0	0	0
		Tiptoe gait	0	4	2	0	0	0	0	2	2	0	0	*	0	2	*	0	0	1	0	0	0
		No abnormalities detected	5	0	3	5	5	5	5	3	2	5	5	*	5	3	*	5	5	2	5	5	5

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing - Days 3 to 7
▲ = orange staining on cage tray liners – Days 5 to 7 inclusive

Table 5 (continued) **Clinical Observations for Recovery Females - Group Incidences**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 8			Day: 9			Day: 10			Day: 11			Day: 12			Day: 13			Day: 14		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	5	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	*	5	5	5
600 ■ ▲	5	Ataxia	0	0	0	0	0	0	0	1	0	0	0	*	0	0	*	0	0	*	0	0	0
		Hunched posture	0	0	0	0	0	0	0	1	0	0	0	*	0	0	*	0	0	*	0	0	0
		Tiptoe gait	0	0	0	0	2	0	0	1	0	0	0	*	0	0	*	0	0	*	0	0	0
		Wet fur	0	3	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	*	0	0	0
		No abnormalities detected	5	2	5	5	3	5	5	4	5	5	5	*	5	5	*	5	5	*	5	5	5

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend or on public holiday
■ = increased salivation detected up to ten minutes after dosing - between Days 8 and 14
▲ = orange staining detected on cage tray liners – Days 8 to 14 inclusive

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 5 (continued) Clinical Observations for Recovery Females - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 15			Day: 16			Day: 17			Day: 18			Day: 19			Day: 20			Day: 21		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	5	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	5	5	5	5
600 ■	5	Ataxia	0	0	0	0	0	0	0	0	0	0	0	*	0	0	*	0	1	0	0	1	1
		Increased salivation	0	0	0	0	2	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		No abnormalities detected	5	5	5	5	3	5	5	5	5	5	5	*	5	5	*	5	4	5	5	4	4

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing - Days 15 to 21 inclusive

Table 5 (continued) Clinical Observations for Recovery Females - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																				
			Day: 22			Day: 23			Day: 24			Day: 25			Day: 26			Day: 27			Day: 28		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	5	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	5	5	5	5
600 ■	5	Increased salivation	0	3	0	0	0	0	0	0	0	0	0	*	0	1	*	0	0	0	0	1	0
		Generalised red/brown stained fur	0	0	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	1
		No abnormalities detected	5	2	5	5	5	5	5	5	5	5	5	*	5	4	*	5	5	5	5	4	4

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing – Days 22 to 28 inclusive

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 5 (continued) Clinical Observations for Recovery Females - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																			
			Day: 29			Day: 30			Day: 31			Day: 32			Day: 33			Day: 34			Day: 35		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	5	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	5	5	5	5
600 ■ ▲	5	Increased salivation	0	0	0	0	0	0	0	1	0	0	1	*	0	2	*	0	5	0	0	5	0
		Generalised red/brown stained fur	1	1	1	1	1	1	1	1	1	1	1	*	0	0	*	0	0	0	0	0	0
		No abnormalities detected	4	4	4	4	4	4	4	4	4	4	3	*	5	3	*	5	0	5	5	0	5

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing – Days 29 to 35 inclusive
▲ = orange staining detected on cage tray liners – Day 29 only

Table 5 (continued) **Clinical Observations for Recovery Females - Group Incidences**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation																			
			Day: 36			Day: 37			Day: 38			Day: 39			Day: 40			Day: 41			Day: 42		
			Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h	Pre	1h	5h
0 (Control)	5	No abnormalities detected	5	5	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	5	5	5	5
600 ■ ▲	5	Increased salivation	0	3	0	0	0	0	0	0	0	0	0	*	0	0	*	0	0	0	0	0	0
		No abnormalities detected	5	2	5	5	5	5	5	5	5	5	5	*	5	5	*	5	5	5	5	5	5

Pre = immediately before dosing
1h = one hour after dosing
5h = five hours after dosing
* = five hour observation not performed at weekend
■ = increased salivation detected up to ten minutes after dosing – Days 36 to 42 inclusive
▲ = orange staining detected on cage tray liners – Days 38 and 41

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 5 (continued) Clinical Observations for Recovery Females - Group Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation													
			Day: 43		Day: 44		Day: 45		Day: 46		Day: 47		Day: 48		Day: 49	
			AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
0 (Control)	5	No abnormalities detected	-	5	5	5	5	5	5	*	5	*	5	5	5	5
600	5	No abnormalities detected	-	5	5	5	5	5	5	*	5	*	5	5	5	5

* = observations not performed at weekend
- = observations not performed in error

Table 5 (continued) **Clinical Observations for Recovery Females - Group Incidences**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation													
			Day: 50		Day: 51		Day: 52		Day: 53		Day: 54		Day: 55		Day: 56	
			AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
0 (Control)	5	No abnormalities detected	5	5	-	5	5	5	5	*	5	*	5	5	5	5
600	5	No abnormalities detected	5	5	-	5	5	5	5	*	5	*	5	5	5	5

* = observations not performed at weekend
- = observations not performed in error

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 6 Summary Incidence of Behavioural Assessments - Males

Pretest

Dose Level (mg/kg/day)	0 (Control)		50	175	600
Number of Animals	10		10	10	10
Number Classified As Observation	0	1	0	0	0
Urination	8	2	10	10	10
Defecation	9	1	10	10	10
Transfer arousal	10	0	10	10	10

The scoring system is outlined in Appendix 1

Table 6 (continued) **Summary Incidence of Behavioural Assessments - Males**

Week 1

Dose Level (mg/kg/day)	0 (Control)		50	175		600	
Number of Animals	10		10	10		10	
Number Classified As Observation	0	1	0	0	1	0	1
Urination	8	2	10	6	4	8	2
Transfer arousal	10	0	10	10	0	10	0

The scoring system is outlined in Appendix 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 6 (continued) Summary Incidence of Behavioural Assessments - Males

Week 2

Dose Level (mg/kg/day)	0 (Control)		50	175	600		
Number of Animals	10		10	10	10		
Number Classified As Observation	0	1	0	0	0	1	2
Urination	7	3	10	10	7	1	2
Defecation	9	1	10	10	8	1	1
Transfer arousal	10	0	10	10	10	0	0

The scoring system is outlined in Appendix 1

Table 6 (continued) **Summary Incidence of Behavioural Assessments - Males**

Week 3

Dose Level (mg/kg/day)	0 (Control)			50	175		600	
Number of Animals	10			10	10		10	
Number Classified As Observation	-1	0	1	0	0	1	0	1
Salivation (slight)	0	10	0	10	9	1	6	4
Urination	0	9	1	10	9	1	8	2
Transfer arousal	2	8	0	10	10	0	10	0

The scoring system is outlined in Appendix 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 6 (continued) Summary Incidence of Behavioural Assessments - Males

Week 4

Dose Level (mg/kg/day)	0 (Control)		50		175	600	
Number of Animals	10		10		10	10	
Number Classified As Observation	0	1	0	1	0	0	1
Urination	9	1	8	2	10	8	2
Defecation	10	0	10	0	10	9	1
Transfer arousal	10	0	10	0	10	10	0

The scoring system is outlined in Appendix 1

Table 6 (continued) **Summary Incidence of Behavioural Assessments - Males**

Week 5

Dose Level (mg/kg/day)	0 (Control)	50	175	600	
Number of Animals	10	10	10	10	
Number Classified As Observation	0	0	0	0	Wt
Gait	10	10	10	9	1
Urination	10	10	10	10	0
Defecation	10	10	10	10	0
Transfer arousal	10	10	10	10	0

The scoring system is outlined in Appendix 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 6 (continued) Summary Incidence of Behavioural Assessments - Males

Week 6

Dose Level (mg/kg/day)	0 (Control)	50	175		600				
Number of Animals	10	10	10		10				
Number Classified As Observation	0	0	0	1	-1	1	0	H	Wt
Gait	10	10	10	0	0	0	9	0	1
Bizarre behaviour	10	10	10	0	0	0	9	1	0
Salivation (slight)	10	10	7	3	0	2	8	0	0
Urination	10	10	10	0	0	1	9	0	0
Transfer arousal	10	10	10	0	1	0	9	0	0

The scoring system is outlined in Appendix 1

H = hunched posture

Table 7 Summary Incidence of Behavioural Assessments - Females

Pretest

Dose Level (mg/kg/day)	0 (Control)		50		175	600	
Number of Animals	10		10		10	10	
Number Classified As Observation	0	1	0	1	0	0	1
Urination	8	2	8	2	10	7	3
Transfer arousal	10	0	10	0	10	10	0

The scoring system is outlined in Appendix 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 7 (continued) Summary Incidence of Behavioural Assessments - Females

Week 1

Dose Level (mg/kg/day)	0 (Control)	50		175			600					
Number of Animals	10	10		10			10					
Number Classified As Observation	0	0	1	0	1	2	0	1	2	A	H	Wt
Gait	10	10	0	10	0	0	5	0	0	0	0	5
Bizarre behaviour	10	10	0	10	0	0	6	0	0	1	3	0
Urination	10	8	2	7	2	1	6	3	1	0	0	0
Transfer arousal	10	10	0	10	0	0	9	1	0	0	0	0

The scoring system is outlined in Appendix 1

A = ataxia
H = hunched posture

Table 7 (continued) **Summary Incidence of Behavioural Assessments - Females**

Week 2

Dose Level (mg/kg/day)	0 (Control)			50		175	600			
Number of Animals	10			10		10	10			
Number Classified As / Observation	0	1	2	0	1	0	0	1	2	Wt
Gait	10	0	0	10	0	10	8	0	0	2
Urination	8	2	0	9	1	10	4	4	2	0
Defecation	8	1	1	10	0	10	9	1	0	0
Transfer arousal	10	0	0	10	0	10	10	0	0	0

The scoring system is outlined in Appendix 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 7 (continued) Summary Incidence of Behavioural Assessments - Females

Week 3

Dose Level (mg/kg/day)	0 (Control)		50		175		600		
Number of Animals	10		10		10		10		
Number Classified As / Observation	0	1	0	1	0	1	0	1	2
Urination	8	2	8	2	8	2	8	2	0
Defecation	9	1	10	0	10	0	6	2	2
Transfer arousal	10	0	10	0	10	0	9	1	0

The scoring system is outlined in Appendix 1

Table 7 (continued) **Summary Incidence of Behavioural Assessments - Females**

Week 4

Dose Level (mg/kg/day)	0 (Control)			50	175			600		
Number of Animals	10			10	10			10		
Number Classified As / Observation	-1	0	1	0	0	1	2	0	1	2
Urination	0	9	1	10	8	1	1	9	1	0
Defecation	0	10	0	10	10	0	0	9	0	1
Transfer arousal	1	9	0	10	10	0	0	10	0	0

The scoring system is outlined in Appendix 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 7 (continued) Summary Incidence of Behavioural Assessments - Females

Week 5

Dose Level (mg/kg/day)	0 (Control)				50	175		600		
Number of Animals	10				10	10		10		
Number Classified As / Observation	-1	0	1	4	0	0	1	-1	0	Wt
Gait	0	10	0	0	10	10	0	0	9	1
Urination	0	9	1	0	10	9	1	0	10	0
Defecation	0	0	9	1	10	10	0	0	10	0
Transfer arousal	1	9	0	0	10	10	0	1	9	0

The scoring system is outlined in Appendix 1

Table 7 (continued) **Summary Incidence of Behavioural Assessments - Females**

Week 6

Dose Level (mg/kg/day)	0 (Control)		50	175			600		
Number of Animals	10		10	10			10		
Number Classified As / Observation	0	1	0	0	1	4	0	1	4
Urination	9	1	10	9	1	0	8	2	0
Defecation	10	0	10	9	1	0	9	0	1
Transfer arousal	10	0	10	10	0	0	10	0	0

The scoring system is outlined in Appendix 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 7 (continued) Summary Incidence of Behavioural Assessments - Females

Day 4 *Post Partum*

Dose Level (mg/kg/day)	0 (Control)		50		175		600			
Number of Animals	9		9		10		10			
Number Classified As Observation	0	1	0	1	0	1	0	1	2	Wt
Gait	9	0	9	0	10	0	9	0	0	1
Salivation (slight)	9	0	9	0	10	0	9	1	0	0
Urination	8	1	8	1	9	1	8	2	0	0
Defecation	9	0	9	0	10	0	9	0	1	0
Transfer arousal	9	0	9	0	8	2	6	4	0	0

The scoring system is outlined in Appendix 1

Table 8 Functional Performance Test for Males - Group Mean Values

Dose Level (mg/kg/day)	Number of Animals		Grip Strength (g)		Motor Activity			
					Overall		Final 20% of Trial	
			Forelimb	Hindlimb	% Activity	% Mobile Activity	% Activity	% Mobile Activity
0 (Control)	5	mean	795	397	29.8	0.0	13.2	0.1
		sd	274	127	17.1	0.1	19.5	0.1
50	5	mean	920	381	20.2	0.0	6.1	0.0
		sd	307	168	14.4	0.0	12.9	0.0
175	5	mean	879	314	26.6	0.0	9.2	0.0
		sd	301	106	6.2	0.0	8.5	0.0
600	5	mean	872	317	15.8	0.0	2.3	0.0
		sd	322	144	9.5	0.0	2.6	0.0

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 9 Functional Performance Test for Females - Group Mean Values

Dose Level (mg/kg/day)	Number of Animals		Grip Strength (g)		Motor Activity			
					Overall		Final 20% of Trial	
			Forelimb	Hindlimb	% Activity	% Mobile Activity	% Activity	% Mobile Activity
0 (Control)	5	mean	941	266	16.7	0.0	0.9	0.0
		sd	237	80	6.5	0.0	1.4	0.0
50	5	mean	996	264	17.9	0.1	3.1	0.0
		sd	184	82	9.9	0.1	1.9	0.0
175	5	mean	980	266	29.9	0.2	16.0	0.0
		sd	249	104	11.6	0.2	15.5	0.0
600	5	mean	886	252	23.5	0.1	2.7	0.0
		sd	289	105	7.0	0.1	4.5	0.0

Table 10 Sensory Reactivity Assessments - Males

Summary Incidence

Dose Level (mg/kg/day)	0 (Control)	50		175			600			
Number of Animals	5	5		5			5			
Number Classified As Observation	0	-1	0	-1	0	1	-2	-1	0	1
Grasp response	5	0	5	0	5	0	0	0	5	0
Vocalisation	5	0	5	0	5	0	0	0	5	0
Toe pinch	5	0	5	1	4	0	0	0	5	0
Tail pinch	5	2	3	2	3	0	1	2	2	0
Finger approach	5	0	5	0	5	0	0	0	5	0
Touch escape	5	0	5	0	4	1	0	0	3	2
Pupil reflex	5	0	5	0	5	0	0	0	5	0
Blink reflex	5	0	5	0	5	0	0	0	5	0
Startle reflex	5	0	5	0	5	0	0	0	5	0

The scoring system is outlined in Appendix 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 11 Sensory Reactivity Assessments - Females

Summary Incidence

Dose Level (mg/kg/day)	0 (Control)	50		175		600	
Number of Animals	5	5		5		5	
Number Classified As Observation	0	0	1	0	1	0	1
Grasp response	5	5	0	5	0	5	0
Vocalisation	5	4	1	4	1	3	2
Toe pinch	5	5	0	5	0	5	0
Tail pinch	5	5	0	5	0	5	0
Finger approach	5	5	0	5	0	5	0
Touch escape	5	5	0	3	2	5	0
Pupil reflex	5	5	0	5	0	5	0
Blink reflex	5	5	0	5	0	5	0

The scoring system is outlined in Appendix 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 12 Bodyweight and Bodyweight Change for Males - Group Mean Values

Dose Level (mg/kg/day)	Number of Animals		Bodyweight (g) At Day								
			1	8	15	22	29	36	43	50	57
0 (Control)	10	mean	300	356	389	423	454	477	481	-	-
		sd	14	19	30	31	39	41	48	-	-
50	10	mean	299	350	386	420	450	472	478	-	-
		sd	14	20	31	31	34	39	42	-	-
175	10	mean	300	353	392	428	459	483	493	-	-
		sd	13	14	21	23	28	29	39	-	-
600	10	mean	299	336	359	387	409	425	420	-	-
		sd	15	21	27	29	34	37	39	-	-
0 (Control) Recovery	5	mean	298	349	384	421	449	479	495	513	528
		sd	13	20	36	42	52	57	61	66	68
600 Recovery	5/4■	mean	298	336	374	409	432	442	442	449	466
		sd	14	5	8	12	17	25	28	37	44

Dose Level (mg/kg/day)	Number of Animals		Bodyweight Change (g) during Week							
			1	2	3	4	5	6	7	8
0 (Control)	10	mean	56	33	34	32	23	4	-	-
		sd	13	13	8	9	6	9	-	-
50	10	mean	51	36	34	30	22	5	-	-
		sd	11	12	5	7	6	12	-	-
175	10	mean	54	39	36	31	24	10	-	-
		sd	9	12	9	8	7	12	-	-
600	10	mean	**38	23	28	*22	16	-5	-	-
		sd	13	11	4	8	7	11	-	-
0 (Control) Recovery	5	mean	51	34	37	28	30	16	18	15
		sd	14	25	8	12	6	10	7	8
600 Recovery	5/4■	mean	38	38	35	19	18	0	7	17
		sd	11	5	4	9	5	8	14	11

- = not applicable
■ = n = 4, Week 4 only
* = significantly different from control group $p<0.05$
** = significantly different from control group $p<0.01$

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 13 Bodyweight and Bodyweight Change for Females - Group Mean Values

Non-Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Bodyweight (g) at Day								
			Prior to Pairing			Gestation				Lactation	
			0	7	14	0	7	14	20	1	4
0 (Control)	10/9•	mean	185	208	235	229	272	316	398	306	320
		sd	14	13	24	15	17	17	16	23	23
50	10/9■	mean	186	205	221	229	272	313	396	302	317
		sd	8	11	11	11	15	19	29	25	25
175	10	mean	186	206	222	224	270	315	397	309	325
		sd	10	8	11	11	15	14	13	15	19
600	10	mean	188	208	222	225	266	306	377	284	298
		sd	7	8	11	10	11	11	17	12	10

Dose Level (mg/kg/day)	Number of Animals		Bodyweight Change (g) during:					
			Prior to Pairing (Week)		Gestation (Days)			Lactation (Days)
			1	2	0-7	7-14	14-20	1-4
0 (Control)	10/9•	mean	23	27	43	45	82	14
		sd	7	25	12	7	14	8
50	10/9■	mean	20	16	43	41	82	15
		sd	10	5	7	5	12	7
175	10	mean	20	17	46	45	81	16
		sd	6	11	7	6	4	7
600	10	mean	20	14	41	40	72	14
		sd	5	5	4	6	11	6

• n = 9 during lactation
■ n = 9 during gestation and lactation

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 13 (continued) Bodyweight and Bodyweight Change for Females - Group Mean Values

Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Bodyweight (g) at Day								
			1	8	15	22	29	36	43	50	57
0 (Control)	5	mean	192	214	230	247	259	270	274	280	286
		sd	14	11	13	10	16	17	14	16	20
600	5	mean	186	209	223	238	251	263	264	263	272
		sd	10	11	14	21	24	22	19	17	15

Dose Level (mg/kg/day)	Number of Animals		Bodyweight Change (g) during Week							
			1	2	3	4	5	6	7	8
0 (Control)	5	mean	22	16	17	12	11	4	6	6
		sd	6	8	13	9	5	8	11	7
600	5	mean	23	14	15	13	12	1	-1	9
		sd	8	6	9	11	4	6	7	8

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 14 Food Consumption for Males - Group Mean Values

Dose Level (mg/kg/day)	Number of Animals	Mean Food Consumption (g/rat/day) during Week							
		1	2	3	4	5	6	7	8
0 (Control)	10	30	29	▲	30	29	26	-	-
50	10	28	28	▲	28	27	24	-	-
		(-7)	(-3)		(-7)	(-7)	(-8)	-	-
175	10	29	29	▲	31	30	27	-	-
		(-3)	(0)		(+3)	(+3)	(+4)	-	-
600	10	27	29	▲	30	31	27	-	-
		(-10)	(0)		(0)	(+7)	(+4)	-	-
0 (Control) Recovery	5	31	28	28	30	30	28	33	31
600 Recovery	5	28	31	31	32	31	30	28	27
		(-10)	(+10)	(+10)	(+7)	(+3)	(+7)	(-15)	(-13)

( ) = % change compared to controls
▲ = data unavailable; non-recovery animals in mating cages
- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 15 Food Consumption for Females - Group Mean Values

Non-Recovery Females

Dose Level (mg/kg/day)	Number of Animals	Mean Food Consumption (g/rat/day) during: Prior to Pairing (Week) 1	Prior to Pairing (Week) 2	Gestation (Days) 0-7	Gestation (Days) 7-14	Gestation (Days) 14-21	Lactation (Days) 1-4
0 (Control)	10/9▲	18	17	21	23	24	36
50	10/9●	18	17	22	24	23	36
		(0)	(0)	(+5)	(+4)	(-4)	(0)
175	10	16	17	22	23	23	40
		(-11)	(0)	(+5)	(0)	(-4)	(+11)
600	10	17	*20	21	23	23	33
		(-6)	(+18)	(0)	(0)	(-4)	(-8)

▲ n = 9 during lactation only
( ) = % change compared to controls
• n = 9 during gestation and lactation phases
* = significantly different from control group $p<0.05$

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 15 (continued) Food Consumption for Females - Group Mean Values

Recovery Females

Dose Level (mg/kg/day)	Number of Animals	Mean Food Consumption (g/rat/day) during Week							
		1	2	3	4	5	6	7	8
0 (Control)	5	18	17	18	19	19	18	21	21
600	5	18	18	19	21	21	19	21	21
		(0)	(+6)	(+6)	(+11)	(+11)	(+6)	(0)	(0)

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 16 Food Efficiency for Males

Dose Level (mg/kg/day)	Number of Animals	Food Efficiency* during Week							
		1	2	3	4	5	6	7	8
0 (Control)	10	0.27	0.16	▲	0.15	0.11	0.02	-	-
50	10	0.26	0.18	▲	0.15	0.12	0.03	-	-
175	10	0.26	0.19	▲	0.14	0.11	0.05	-	-
600	10	0.20	0.11	▲	0.10	0.07	-0.03	-	-
0 (Control) Recovery	5	0.24	0.17	0.19	0.13	0.14	0.08	0.08	0.07
600 Recovery	5	0.19	0.18	0.16	0.08	0.08	0.00	0.04	0.09

$$\text{* Food Efficiency} = \frac{\text{Group mean bodyweight gain (g/rat)}}{\text{Group mean food consumption (g/rat/day) x number of days}}$$

▲ = data not available; non-recovery animals in mating cages
- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 17 Food Efficiency for Females

Non-Recovery Females

Dose Level (mg/kg/day)	Number of Animals	Food Efficiency* during: Prior to Pairing (Week)		Gestation (Days)			Lactation (Days)
		1	2	0-7	7-14	14-20	1- 4
0 (Control)	10	0.18	0.23	0.29	0.28	-	-
50	10	0.16	0.13	0.28	0.24	-	-
175	10	0.18	0.14	0.30	0.28	-	-
600	10	0.17	0.10	0.28	0.25	-	-

* Food Efficiency = $\frac{\text{Group mean bodyweight gain (g/rat)}}{\text{Group mean food consumption (g/rat/day) x number of days}}$

- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 17 (continued) Food Efficiency for Females

Recovery Females

Dose Level (mg/kg/day)	Number of Animals	Food Efficiency* during Week							
		1	2	3	4	5	6	7	8
0 (Control)	5	0.17	0.13	0.13	0.09	0.08	0.03	0.04	0.04
600	5	0.18	0.11	0.11	0.09	0.08	0.01	-0.01	0.06

* Food Efficiency = $\frac{\text{Group mean bodyweight gain (g/rat)}}{\text{Group mean food consumption (g/rat/day) x number of days}}$

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 18 Water Consumption for Males - Group Mean Values

Non – Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Mean Water Consumption (g/rat/day) on Day:																												
			8	9	10	11	12	13	14	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37▲	38	39	40	41	42
0 (Control)	10	mean	38	39	37	37	41	29	41	37	40	34	41	36	36	39	39	38	35	39	37	40	45	33	30	38	39	38	30	38
50	10	mean	38	42	39	37	41	31	45	39	41	35	45	36	35	45	38	42	39	38	36	39	47	32	30	37	38	37	35	39
175	10	mean	38	44	43	42	47	32	50	44	45	44	52	41	41	44	42	48	47	44	37	47	55	36	34	43	42	43	39	51
600	10	mean	42	45	43	40	43	32	50	43	44	40	46	44	42	43	42	43	40	43	39	43	49	39	28	44	37	42	39	46

▲ = animals in cages A1, C1, E1 and G1 in met cages overnight

Table 18 (continued) **Water Consumption for Males - Group Mean Values**

Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Mean Water Consumption (g/rat/day) on Day:																									
			8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
0 (Control)	5	mean	34	40	39	35	39	30	42	29	39	34	34	40	36	39	36	41	33	41	33	35	34	39	36	34	36	36
600	5	mean	47	50	47	45	49	38	50	41	45	42	42	45	45	43	43	45	44	47	47	41	43	41	46	34	40	44

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 18 (continued) Water Consumption for Males - Group Mean Values

Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Mean Water Consumption (g/rat/day) on Day:																					
			34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51▲	52	53	54	55	56
0 (Control)	5	mean	34	42	31	35	38	36	38	34	39	36	40	38	43	38	39	37	41	3	57	64	41	39	36
600	5	mean	48	51	39	48	42	42	43	42	44	35	36	33	39	32	36	37	41	1	50	39	38	38	38

▲ = animals in met cages overnight

Table 19 Water Consumption for Females - Group Mean Values

Non – Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Mean Water Consumption (g/rat/day) on Maturation Day:						
			8	9	10	11	12	13	14
0 (Control)	10	mean	22	25	23	22	29	19	30
50	10	mean	23	25	26	23	30	20	28
175	10	mean	21	26	26	22	26	21	31
600	10	mean	30	33	33	33	30	24	38

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 19 (continued) Water Consumption for Females - Group Mean Values

Non – Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Mean Water Consumption (g/rat/day) on Gestation Day:																			
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
0 (Control)	10	mean	25	31	34	36	34	34	35	35	38	40	38	37	39	38	39	44	47	47	51	44	41
50	10	mean	29	34	36	39	36	37	39	49	39	42	42	39	41	43	41	47	49	51	48	48	43
175	10	mean	30	35	36	41	38	39	38	40	53	45	43	*44	41	43	44	49	53	49	54	49	*49
600	10	mean	*36	**40	43	45	**44	**44	**50	**48	**53	51	47	**55	**59	**55	**56	**60	**62	55	*60	55	*50

* =significantly different from control group p<0.05
** = significantly different from control group p<0.01
*** = significantly different from control group p<0.001

Table 19 (continued) Water Consumption for Females - Group Mean Values

Non – Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Mean Water Consumption (g/rat/day) on Lactaion Day:			
			1	2	3	4
0 (Control)	10	mean	48	55	60	60
50	10	mean	49	58	62	67
175	10	mean	56	63	67	73
600	10	mean	52	59	68	67

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 19 (continued) Water Consumption for Females - Group Mean Values

Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Mean Water Consumption (g/rat/day) on Day:																								
			8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
0 (Control)	5	mean	24	24	26	25	29	18	32	25	29	26	28	30	27	28	26	31	26	25	25	29	30	27	29	27	27
600	5	mean	28	33	37	35	33	26	39	37	36	35	36	41	34	43	38	40	34	42	39	38	39	36	38	33	39

Table 19 (continued) **Water Consumption for Females - Group Mean Values**

Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Mean Water Consumption (g/rat/day) on Day:																							
			33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56
0 (Control)	5	mean	26	28	36	25	26	27	30	29	23	27	27	29	25	31	29	43	25	27	29	31	30	29	26	27
600	5	mean	33	38	43	29	38	37	40	30	30	31	31	25	27	34	29	26	26	32	30	26	28	33	29	25

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 20 Haematology for Males - Group Mean Values

Day 14 - Non-Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
0 (Control)	5	mean	14.7	7.33	42.0	20.1	57.4	35.0	12.7
		sd	0.9	0.30	2.2	0.7	1.8	0.5	2.4
50	5	mean	15.0	7.60	43.1	19.8	56.6	34.9	11.4
		sd	0.3	0.24	0.6	0.4	1.7	0.9	2.1
175	5	mean	15.1	7.46	43.5	20.4	58.6	34.8	12.3
		sd	0.3	0.60	1.7	1.6	3.2	0.9	1.5
600	5	mean	14.9	7.62	43.5	19.6	57.2	34.3	14.4
		sd	0.6	0.54	1.9	1.0	2.9	0.1	3.2

Dose Level (mg/kg/day)	Number of Animals		Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
			Neut	Lymph	Mono	Eos	Bas			
0 (Control)	5	mean	1.39	11.21	0.03	0.05	0.00	17.6	1008	16.0
		sd	0.40	2.21	0.07	0.12	0.00	2.1	58	2.4
50	5	mean	1.46	9.86	0.00	0.03	0.00	16.5	914	15.3
		sd	0.60	2.11	0.00	0.08	0.00	1.4	46	1.6
175	5	mean	1.96	10.23	0.00	0.10	0.00	16.9	1021	15.0
		sd	1.21	0.34	0.00	0.06	0.00	1.8	102	1.5
600	5	mean	2.47	11.81	0.00	0.09	0.00	15.0	914	13.9
		sd	1.04	3.25	0.00	0.09	0.00	2.2	87	2.9

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 20 (continued) Haematology for Males - Group Mean Values

Day 42 - Non-Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
0 (Control)	5	mean	15.8	8.46	46.6	18.7	54.8	34.0	13.4
		sd	0.7	0.32	1.7	0.6	1.6	0.4	1.3
50	5	mean	15.9	8.54	47.0	18.6	55.0	33.7	11.4
		sd	0.4	0.28	1.7	0.6	1.9	0.5	1.2
175	5	mean	16.1	8.43	46.6	19.1	55.4	34.5	11.9
		sd	0.4	0.42	0.7	1.3	3.2	1.0	2.4
600	5	mean	16.0	8.80	47.9	18.3	54.4	33.5	14.5
		sd	0.3	0.34	0.5	0.8	1.9	0.3	2.7

Dose Level (mg/kg/day)	Number of Animals		Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
			Neut	Lymph	Mono	Eos	Bas			
0 (Control)	5	mean	2.02	11.21	0.00	0.13	0.00	17.1	774	13.4
		sd	0.47	0.97	0.00	0.16	0.00	3.8	85	3.5
50	5	mean	1.76	9.41	0.00	0.21	0.00	17.2	711	13.5
		sd	0.73	1.52	0.00	0.16	0.00	2.3	44	1.5
175	5	mean	2.06	9.76	0.00	0.13	0.00	14.8	800	11.5
		sd	1.50	1.46	0.00	0.10	0.00	4.1	40	1.8
600	5	mean	1.80	12.46	0.00	0.26	0.00	17.1	739	13.5
		sd	1.57	2.17	0.00	0.11	0.00	2.4	46	2.1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 20 (continued) Haematology for Males - Group Mean Values

Day 56 - Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
0 (Control)	5	mean	15.7	8.62	47.0	18.2	54.6	33.4	11.7
		sd	0.5	0.30	2.2	0.6	1.5	0.6	1.7
600	5	mean	15.8	9.01	47.8	17.5	53.2	33.0	12.4
		sd	0.6	0.24	1.6	0.3	0.8	0.2	2.3

Dose Level (mg/kg/day)	Number of Animals		Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
			Neut	Lymph	Mono	Eos	Bas			
0 (Control)	5	mean	1.64	9.95	0.00	0.12	0.00	16.5	746	15.6
		sd	0.79	1.34	0.00	0.15	0.00	0.7	83	1.0
600	5	mean	1.67	10.61	0.00	0.16	0.00	17.7	793	15.6
		sd	0.92	2.50	0.00	0.13	0.00	2.9	50	3.1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 21 Haematology for Females - Group Mean Values

Day 14 - Non-Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
0 (Control)	5	mean	14.5	7.17	40.6	20.2	56.5	35.7	8.1
		sd	0.5	0.35	1.6	1.0	2.6	0.3	1.8
50	5	mean	14.7	7.44	41.2	19.7	55.8	35.7	8.2
		sd	0.5	0.37	1.9	0.4	1.0	0.7	2.6
175	5	mean	14.5	7.29	40.7	19.9	56.0	35.7	10.2
		sd	0.5	0.33	1.3	0.5	1.2	0.4	2.9
600	5	mean	14.7	7.38	41.3	19.9	56.0	35.5	8.3
		sd	0.5	0.22	1.2	0.4	1.0	0.4	1.5

Dose Level (mg/kg/day)	Number of Animals		Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
			Neut	Lymph	Mono	Eos	Bas			
0 (Control)	5	mean	0.68	7.43	0.00	0.02	0.00	17.8	973	16.0
		sd	0.12	1.75	0.00	0.04	0.00	2.8	37	0.4
50	5	mean	0.56	7.50	0.00	0.14	0.00	17.6	906	15.3
		sd	0.19	2.45	0.00	0.06	0.00	3.9	236	1.3
175	5	mean	2.04	8.07	0.00	0.08	0.00	16.3	924	14.7
		sd	2.16	2.72	0.00	0.05	0.00	2.4	88	1.6
600	5	mean	0.78	7.52	0.00	0.04	0.00	16.9	991	15.6
		sd	0.21	1.50	0.00	0.07	0.00	2.9	131	1.1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 21 (continued) Haematology for Females - Group Mean Values

Day 5 *post partum* - Non-Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
0 (Control)	5	mean	12.7	6.52	37.3	19.4	57.0	34.0	7.3
		sd	0.8	0.36	2.6	0.5	1.6	0.5	2.8
50	5	mean	11.8	6.22	35.7	19.0	57.4	33.0	6.1
		sd	0.5	0.33	1.8	0.7	1.9	0.7	0.8
175	5	mean	12.3	6.18	36.9	20.0	59.4	33.5	9.0
		sd	0.5	0.24	1.7	0.8	1.9	0.7	4.4
600	5	mean	12.6	6.69	38.3	18.9	57.4	33.0	7.0
		sd	0.5	0.13	1.8	0.5	2.1	0.7	1.8

Dose Level (mg/kg/day)	Number of Animals		Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
			Neut	Lymph	Mono	Eos	Bas			
0 (Control)	5	mean	1.10	6.11	0.00	0.05	0.00	16.4	705	12.8
		sd	1.17	1.87	0.00	0.07	0.00	1.4	121	1.7
50	5	mean	1.15	4.88	0.00	0.04	0.00	15.3	825	12.3
		sd	0.60	0.58	0.00	0.06	0.00	1.1	109	1.9
175	5	mean	2.09	6.83	0.00	0.06	0.00	16.7	746	11.3
		sd	1.87	2.57	0.00	0.07	0.00	2.4	160	2.9
600	5	mean	1.33	5.67	0.00	0.00	0.00	16.0	662	11.8
		sd	0.94	1.30	0.00	0.00	0.00	2.0	150	0.2

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 21 (continued) Haematology for Females - Group Mean Values

Day 56 - Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
0 (Control)	5	mean	14.7	7.85	42.9	18.7	54.6	34.2	8.6
		sd	0.7	0.32	1.7	1.0	2.3	0.3	1.8
600	5	mean	14.2	8.30	42.7	17.1	51.6	33.2	8.6
		sd	0.5	0.33	1.2	0.8	1.8	0.5	1.1

Dose Level (mg/kg/day)	Number of Animals		Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
			Neut	Lymph	Mono	Eos	Bas			
0 (Control)	5	mean	1.16	7.37	0.00	0.07	0.00	15.1	793	13.3
		sd	0.30	1.98	0.00	0.08	0.00	1.2	111	0.8
600	5	mean	0.77	7.75	0.00	0.06	0.00	16.2	903	15.3
		sd	0.33	1.15	0.00	0.06	0.00	2.7	84	1.7

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 22 Blood Chemistry for Males - Group Mean Values

Day 14 - Non-Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)
0 (Control)	5	mean	35	168	6.30	3.74	1.46	147	4.65	104
		sd	3	21	0.20	0.11	0.11	1	0.25	1
50	5	mean	33	166	6.71	3.79	1.31	148	4.53	104
		sd	4	21	0.34	0.08	0.16	3	0.43	2
175	5	mean	37	167	**7.03	**4.05	1.36	149	4.49	103
		sd	6	4	0.21	0.10	0.07	1	0.13	2
600	5	mean	34	163	*6.75	**4.02	1.47	149	4.43	104
		sd	3	16	0.23	0.17	0.06	1	0.22	2

Dose Level (mg/kg/day)	Number of Animals		Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
0 (Control)	5	mean	2.75	2.2	69	44	404	0.77	73	0.12
		sd	0.09	0.3	5	8	78	0.02	9	0.04
50	5	mean	2.76	2.4	70	45	474	0.78	74	0.15
		sd	0.15	0.2	7	5	63	0.06	9	0.02
175	5	mean	2.88	2.3	66	45	432	**0.88	73	0.07
		sd	0.11	0.3	4	2	89	0.04	18	0.02
600	5	mean	2.77	2.4	76	45	375	**0.88	66	0.11
		sd	0.18	0.1	9	8	56	0.02	10	0.03

* = significantly different from control group $p<0.05$
** = significantly different from control group $p<0.01$

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 22 (continued) Blood Chemistry for Males - Group Mean Values

Day 42 - Non-Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl- (mmol/l)
0 (Control)	5	mean	30	165	6.71	3.66	1.21	147	4.59	104
		sd	3	15	0.45	0.13	0.14	1	0.18	1
50	5	mean	29	155	6.65	3.57	1.17	147	4.58	104
		sd	3	16	0.22	0.13	0.10	1	0.25	1
175	5	mean	29	155	7.33	3.80	1.08	147	*5.05	*102
		sd	5	10	0.20	0.23	0.12	1	0.32	1
600	5	mean	27	144	6.86	3.76	1.22	146	4.84	102
		sd	3	7	0.36	0.12	0.10	1	0.18	1

Dose Level (mg/kg/day)	Number of Animals		Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
0 (Control)	5	mean	2.58	1.9	74	40	308	0.79	66	0.22
		sd	0.19	0.4	8	2	75	0.03	13	0.04
50	5	mean	2.40	1.9	74	44	334	0.79	64	0.20
		sd	0.31	0.3	10	6	53	0.05	13	0.03
175	5	mean	2.61	2.2	67	43	302	0.84	69	0.15
		sd	0.13	0.2	8	7	53	0.05	14	0.06
600	5	mean	2.63	2.1	78	40	304	0.85	63	0.25
		sd	0.10	0.2	9	11	61	0.03	20	0.05

* = significantly different from control group $p<0.05$

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 22 (continued) Blood Chemistry for Males - Group Mean Values

Day 56 - Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
0 (Control)	5	mean	33	144	6.64	3.50	1.12	147	5.28	103
		sd	4	7	0.26	0.13	0.12	2	0.33	1
600	5	mean	40	141	7.43	3.92	1.12	148	5.47	101
		sd	6	7	0.21	0.10	0.09	2	0.27	1

Dose Level (mg/kg/day)	Number of Animals		Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
0 (Control)	5	mean	2.62	2.1	87	45	355	0.80	62	0.09
		sd	0.08	0.1	5	6	20	0.02	7	0.06
600	5	mean	2.61	2.2	80	43	284	0.83	77	0.12
		sd	0.27	0.1	7	4	98	0.03	9	0.03

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 23 Blood Chemistry for Females - Group Mean Values

Day 14 -Non-Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
0 (Control)	5	mean	37	159	6.25	3.84	1.59	149	4.59	106
		sd	6	9	0.11	0.07	0.06	1	0.32	1
50	5	mean	35	166	6.55	*3.99	1.57	149	4.74	105
		sd	4	6	0.17	0.04	0.10	1	0.42	1
175	5	mean	**26	159	6.49	*3.99	1.62	147	4.78	*104
		sd	3	8	0.30	0.08	0.20	2	0.44	1
600	5	mean	**25	*138	*6.78	***4.14	1.58	*146	4.57	***102
		sd	4	15	0.35	0.13	0.13	1	0.37	1

Dose Level (mg/kg/day)	Number of Animals		Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
0 (Control)	5	mean	2.78	1.8	73	41	269	0.84	75	0.07
		sd	0.13	0.2	7	8	13	0.07	10	0.04
50	5	mean	2.74	2.0	73	45	327	0.84	88	0.11
		sd	0.12	0.4	7	3	102	0.03	8	0.08
175	5	mean	2.74	2.1	58	32	269	0.81	70	0.10
		sd	0.14	0.4	9	7	50	0.03	12	0.02
600	5	mean	2.75	2.4	68	31	237	0.83	92	0.09
		sd	0.10	0.3	9	7	56	0.05	23	0.05

* = significantly different from control group $p<0.05$
** = significantly different from control group $p<0.01$
*** = significantly different from control group $p<0.001$

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 23 (continued) Blood Chemistry for Females - Group Mean Values

Day 5 *Post Partum* -Non-Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
0 (Control)	5	mean	42	135	5.60	3.18	1.32	148	5.10	102
		sd	9	20	0.37	0.20	0.15	1	0.27	1
50	5	mean	46	131	5.76	3.25	1.30	150	5.29	104
		sd	6	8	0.29	0.17	0.12	1	0.31	1
175	5	mean	43	123	5.84	3.20	1.22	149	5.01	104
		sd	11	12	0.18	0.17	0.16	2	0.89	2
600	5	mean	37	127	5.78	3.36	1.39	150	4.93	105
		sd	8	9	0.23	0.09	0.14	2	0.39	3

Dose Level (mg/kg/day)	Number of Animals		Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
0 (Control)	5	mean	2.51	1.7	83	64	183	0.78	55	0.03
		sd	0.08	0.4	18	16	49	0.13	6	0.04
50	5	mean	2.66	1.6	101	91	263	0.81	72	0.04
		sd	0.08	0.6	55	38	182	0.04	4	0.02
175	5	mean	2.44	1.6	87	90	208	0.82	62	0.05
		sd	0.09	0.4	36	32	52	0.21	11	0.03
600	5	mean	2.52	1.6	89	72	162	0.80	68	0.09
		sd	0.09	0.2	16	15	68	0.02	11	0.05

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 23 (continued) Blood Chemistry for Females - Group Mean Values

Day 56 - Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
0 (Control)	5	mean	42	151	7.04	3.93	1.27	147	5.15	102
		sd	6	7	0.48	0.18	0.10	1	0.25	1
600	5	mean	43	148	7.86	4.52	1.36	147	4.78	102
		sd	8	11	0.49	0.16	0.11	1	0.27	1

Dose Level (mg/kg/day)	Number of Animals		Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
0 (Control)	5	mean	2.59	1.9	94	39	179	0.89	68	0.12
		sd	0.23	0.2	13	2	75	0.05	11	0.01
600	5	mean	2.78	1.8	93	47	182	0.96	82	0.13
		sd	0.10	0.4	6	5	51	0.03	11	0.02

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 24 Urinalytical Findings for Males - Summary Incidence

Dose Level (mg/kg/day)	Number of Animals		Volume (ml)	Specific Gravity	Incidence							
					pH			Protein		Glucose	Ketones	
					6	7	8	0	1+	0	0	1+
0 (Control)	5	mean sd	19.1 12.4	1.023 0.012	2	3	0	0	5	5	2	3
50	5	mean sd	20.6 10.4	1.018 0.005	2	3	0	1	4	5	0	5
175	5	mean sd	27.8 4.6	1.016 0.004	1	4	0	2	3	5	0	5
600	5	mean sd	24.6 15.9	1.023 0.007	3	2	0	1	4	5	0	5
0 (Control) Recovery Group	5	mean sd	13.2 7.3	1.028 0.010	1	3	1	0	5	5	0	5
600 Recovery Group	5	mean sd	8.6 3.0	1.032 0.008	1	3	1	0	5	5	0	5

Protein: 0 = Negative
1 + = 0.3 g/l

Glucose: 0 = normal

Ketones: 0 = negative
1+ = positive result

sd = standard deviation

Dose Level (mg/kg/day)	Number of Animals	Incidence								
		Urobilinogen	Bilirubin	Blood (Erythrocytes)	Blood (Haemoglobin)			Reducing Substances (%)		Appearance
		0	0	0	0	1+	2+	0	0.25	NAD
0 (Control)	5	5	5	5	5	0	0	4	1	5
50	5	5	5	5	5	0	0	5	0	5
175	5	5	5	5	5	0	0	5	0	5
600	5	5	5	5	5	0	0	5	0	5
0 (Control) Recovery Group	5	5	5	5	5	0	0	5	0	5
600 Recovery Group	5	5	5	5	1	3	1	3	2	5

Urobilinogen: 0 = normal

Bilirubin: 0 = negative

Blood (erythrocytes and haemoglobin): 0 = negative
Blood (haemoglobin): 1+ = ca 10 Ery/µl
2+ = ca 25 Ery/µl
Appearance: NAD = no abnormalities detected

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 25 Mating Performance and Fertility - Group values

Dose Group (mg/kg/day)	Number of Males Paired	Number of Females			Pre-Coital Interval (Days)				Mating Index (%)	Pregnancy Index (%)
		Paired	Mated	Pregnant	1	2	3	4		
0 (Control)	10	10	10	10	4	4	1	1	100	100
50	10	10	10	9	5	3	1	1	100	90
175	10	10	10	10	3	6	0	1	100	100
600	10	10	10	10	1	5	2	2	100	100

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 26 Summary Incidence of Gestation Lengths

Dose Group (mg/kg/day)	Number of Pregnant Females	Gestation Lengths (Days)			Females with Live Offspring	Parturition Index (%)
		22	22½	23		
0 (Control)	10	5	1	4	9	90
50	9	3	2	4	9	100
175	10	2	4	4	10	100
600	10	1	3	6	10	100

Table 27 Litter and Bodyweight Data - Group Mean Litter Values

Dose Group (mg/kg/day)	Number of litters		Number of Corpora Lutea	Number of Implantation Sites	Total number of Offspring Born	Number of Live Offspring		Litter Weight (g)		Offspring Weight (g)				Mean Offspring bodyweight change (g)		
						Day 1	Day 4	Day 1	Day 4	Day 1		Day 4		Days 1 - 4		
										Male	Female	Male	Female	Male	Females	Combined
0 (Control)	9/8●	mean	16.4	14.0	13.7	13.2	13.0	93.1	135.8	7.3	6.9	10.8	10.4	3.5	3.5	3.5
		sd	3.9	3.7	3.4	3.2	3.0	21.3	29.0	0.7	0.7	1.1	1.1	0.6	0.7	0.6
50	9/8●	mean	16.4	15.8	14.6	14.1	14.1	97.9	146.3	7.1	6.8	10.5	10.2	3.5	3.4	3.4
		sd	2.5	1.4	1.7	1.7	1.7	13.9	19.7	0.6	0.6	1.0	0.9	0.7	0.5	0.6
175	10	mean	17.0	15.4	14.3	14.1	14.1	98.5	149.5	7.2	6.8	10.9	10.4	3.7	3.5	3.6
		sd	2.4	0.7	1.1	1.2	1.2	12.3	18.1	0.8	0.8	1.1	1.2	0.4	0.4	0.4
600	10	mean	17.8	15.0	13.7	13.2	13.0	82.9	115.7	6.5	6.2	**9.2	**8.8	**2.6	**2.6	**2.6
		sd	2.6	2.6	2.0	1.3	1.2	9.5	14.1	0.9	0.9	1.1	1.2	0.5	0.4	0.4

● = n = 8 for number of implantation sites
* = significantly different from control group $p<0.05$
** = significantly different from control group $p<0.01$

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 28 Implantation Losses and Survival Indices - Group Mean Litter Values

Dose Group (mg/kg/day)	Number of litters		Pre- Implantation Loss (%)	Post -Implantation Loss (%)	Live Birth Index	Viability Index
0 (Control)	9/8●	mean	15.6	4.0	97.2	98.6
		sd	9.7	6.7	4.6	2.8
50	9/8●	mean	6.9	5.5	97.0	100.0
		sd	6.9	5.3	3.6	0.0
175	10	mean	8.3	7.2	98.6	100.0
		sd	9.3	4.8	3.0	0.0
600	10	mean	15.0	7.4	96.3	98.6
		sd	13.3	6.3	5.8	3.0

● = n = 8 for pre and post implantation loss

Table 29 Sex Ratio - Group Mean Litter Values

Dose Group (mg/kg/day)	Number of litters		Sex Ratio (*Post Partum*) Day: At birth †			1			4		
			Male	Female	% Male	Male	Female	% Male	Male	Female	% Male
0 (Control)	9	Mean	7.3	6.1	54.7	7.1	6.1	54.1	7.0	6.0	54.2
		SD	2.1	1.8	7.3	2.0	1.8	7.0	1.8	1.7	6.3
50	9	Mean	6.8	7.4	47.6	6.8	7.3	47.9	6.8	7.3	47.9
		SD	3.2	3.1	22.1	3.2	3.1	22.3	3.2	3.1	22.3
175	10	Mean	6.6	7.5	46.4	6.6	7.5	46.4	6.6	7.5	46.4
		SD	2.1	1.8	13.8	2.1	1.8	13.8	2.1	1.8	13.8
600	10	Mean	6.0	7.4	44.1	5.9	7.3	44.1	5.7	7.3	43.2
		SD	2.2	1.6	13.9	2.2	1.6	14.5	2.2	1.6	14.6

† = values do not include offspring which were found dead or missing between pre-day 1 and identification on Day 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 30 Summary Incidence of Clinical Observations - Offspring

Dose Level (mg/kg/day)	Number of Females with Litters	Clinical Observations	Numbers of Litters and Offspring per Litter Affected *(Post Partum)* Day: PD1		1		2		3		4		5	
			Number of Litters	Number of Offspring	Number of Litters	Number of Offspring	Number of Litters	Number of Offspring	Number of Litters	Number of Offspring	Number of Litters	Number of Offspring	Number of Litters	Number of Offspring
0 (Control)	9	Bruising on snout	1	1M	1	1M	0	-	0	-	0	-	0	-
		Small	0	-	1	1F	0	-	0	-	0	-	0	-
		Missing	0	-	1	1*	1	1F	0	-	0	-	0	-
		Found Dead	0	-	0	-	1	1M	0	-	0	-	0	-
		No abnormalities detected	8	-	6	-	7	-	9	-	9	-	9	-
50	9	Bruise on head	1	1F	0	-	0	-	0	-	0	-	0	-
		Small	0	-	1	1F	0	-	0	-	0	-	0	-
		Wound on back	0	-	0	-	0	-	0	-	1	1F	1	1F
		Missing	0	-	3	3*	0	-	0	-	0	-	0	-
		No abnormalities detected	8	-	6	-	9	-	9	-	8	-	8	-
175	10	Weak	1	1F	0	-	0	-	0	-	0	-	0	-
		Missing	0	-	2	2*	0	-	0	-	0	-	0	-
		Found Dead	0	-	0	-	0	-	0	-	0	-	1	2F
		No abnormalities detected	9	-	8	-	10	-	10	-	10	-	9	-
600	10	Atrietic tail	1	1F	1	1F	1	1F	1	1F	1	1F	0	-
		No tail	0	-	0	-	0	-	0	-	0	-	1	1F
		Small	0	-	1	1M	1	1M	1	1M	1	1M	1	1M
		Missing	0	-	3	3*	0	-	0	-	0	-	1	1F
		Found Dead	0	-	1	1M	1	1M	0	-	1	1M	0	-
		Cut on nose	0	-	0	-	0	-	1	1F	1	1F	1	1F
		No abnormalities detected	9	-	5	-	7	-	8	-	7	-	7	-

M = male
F = female
PD1 = pre-day 1
* = sex undetermined

Table 31 Offspring Reflexological Responses - Group Mean Values

Dose Level (mg/kg/day)	Number of Litters		Surface Righting Reflex (% passed)
0 (Control)	9	mean	89.3
		sd	8.4
50	9	mean	94.0
		sd	8.0
175	10	mean	98.0
		sd	3.2
600	10	mean	96.3
		sd	5.6

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 32 Necropsy Findings of Offspring - Group Incidences

	Dose Level (mg/kg/day)			
	0 (control)	50	175	600
Interim deaths	3 M (3)	1F (1)	2F (1)	4M, 1F (3)
Autolysis	2M	1F	2F	1M, 1F
No abnormalities detected	1M	-	-	3M
Terminal kill	63M, 54F (9)	61M, 66F (9)	66M, 73F (10)	57M, 73F (10)
Cut on nose	-	-	-	1F (1)
Extra lobe on right lung	-	-	-	1M (1)
Small	-	-	-	1M (1)
No tail	-	-	-	1F (1)
Wound on back	-	1F (1)	-	-
Liver: mottled	-	1F (1)	-	-
No abnormalites detected	63M, 54F (9)	61M, 64F (7)	66M, 73F (10)	55M, 71F (7)

M = male
F = female
( ) = litters affected

Table 33 Necropsy Findings of Males - Group Incidences

Terminal Kill

	Dose Level (mg/kg/day)					
	0 (control)	50	175	600	Recovery control	Recovery 600
Number of animals examined at terminal kill	10	10	10	10	5	5
Bladder: filled with red fluid	0	0	0	1	0	0
Left testes and epididymide: small	0	0	0	1	0	0
Kidneys: hydronephrosis	0	0	1	0	0	0
No abnormalities detected	10	10	9	8	5	5

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 34 Necropsy Findings of Females - Group Incidences

Interim Death

	Dose Level (mg/kg/day)					
	0 (control)	50	175	600	Recovery control	Recovery 600
Number of animals killed *in extremis*:	1	0	0	0	0	0
Adrenal glands: pale	1	N/A	N/A	N/A	N/A	N/A
15 foetuses found in uterus, 2 foetuses and placenti positioned close to bifercation of uterine horns.	1	N/A	N/A	N/A	N/A	N/A

Terminal Kill

	Dose Level (mg/kg/day)					
	0 (control)	50	175	600	Recovery control	Recovery 600
Number of animals examined at terminal kill	9	10	10	10	5	5
Intestines: gaseous distension	0	0	1	0	0	0
No abnormalities detected	9	10	9	10	5	5

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 35 Absolute Organ Weights for Males - Group Mean Values

Non-Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Bodyweight (g) at Terminal Kill	Organ Weight (g)			
				Adrenals	Brain	Epididymides	Heart
0 (Control)	5 (10)	mean	481	0.0597	2.0662	1.3949	1.6516
		sd	48	0.0066	0.0784	0.0891	0.2124
50	5 (10)	mean	478	0.0570	2.0263	1.3105	1.6271
		sd	42	0.0071	0.0707	0.1145	0.1934
175	5 (10)	mean	493	0.0621	2.0290	1.3227	1.5413
		sd	39	0.0090	0.1040	0.1049	0.2020
600	5 (10)▲	mean	420	0.0562	2.0137	1.2309	1.4955
		sd	39	0.0088	0.0994	0.1639	0.3098

Dose Level (mg/kg/day)	Number of Animals		Organ Weight (g)				
			Kidneys	Liver	Spleen	Testes	Thymus
0 (Control)	5 (10)	mean	3.5371	15.9549	0.7372	3.5535	0.4070
		sd	0.2227	2.4203	0.0523	0.2613	0.0936
50	5 (10)	mean	3.5541	15.4940	0.7379	3.4832	0.3691
		sd	0.4864	2.0485	0.0849	0.2834	0.0867
175	5 (10)	mean	3.9777	18.5157	0.7500	3.6588	0.3760
		sd	0.6827	2.0827	0.1396	0.2168	0.0723
600	5 (10)	mean	3.3909	17.7000	0.6475	3.3874	0.3442
		sd	0.4783	3.0294	0.1016	0.4670	0.0327

( ) = number of animals used to calculate mean/sd bodyweights and reproductive organ weights
sd = standard deviation
▲ = n=4 for adrenals only

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 35 (continued) Absolute Organ Weights for Males - Group Mean Values

Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Bodyweight (g) at Terminal Kill	Organ Weight (g)			
				Adrenals	Brain	Epididymides	Heart
0 (Control)	5	mean	528	0.0595	2.1296	1.4453	1.7907
		sd	68	0.0094	0.1850	0.1088	0.1343
600	5	mean	466	0.0646	2.0438	1.3439	1.5939
		sd	44	0.0041	0.0831	0.1581	0.1990

Dose Level (mg/kg/day)	Number of Animals		Organ Weight (g)				
			Kidneys	Liver	Spleen	Testes	Thymus
0 (Control)	5	mean	3.7448	17.1954	0.8713	3.6146	0.3724
		sd	0.3363	1.8051	0.0900	0.3092	0.0997
600	5	mean	3.6694	17.8218	*0.7441	3.6361	0.3590
		sd	0.4708	2.3789	0.0325	0.2830	0.0430

* = significantly different from control group $p<0.05$

Table 36 Absolute Organ Weights for Females - Group Mean Values

Non-Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Bodyweight (g) at Terminal Kill	Organ Weight (g)			
				Adrenals	Brain	Ovaries	Heart
0 (Control)	5 (9)	mean	319	0.0847	1.8255	0.1352	1.0781
		sd	23	0.0148	0.0828	0.0307	0.0843
50	5 (9)●	mean	314	0.0764	1.9098	0.1322	1.0824
		sd	19	0.0144	0.0670	0.0170	0.0601
175	5 (10)	mean	326	0.0946	1.9354	0.1268	1.1061
		sd	21	0.0114	0.0562	0.0147	0.0742
600	5 (10)	mean	298	0.0668	1.7454	0.1351	0.9787
		sd	8	0.0089	0.1283	0.0481	0.1030

Dose Level (mg/kg/day)	Number of Animals		Organ Weight (g)			
			Kidneys	Liver	Spleen	Thymus
0 (Control)	5 (9)	mean	2.0980	13.6037	0.5978	0.3543
		sd	0.1743	1.1109	0.0718	0.0632
50	5 (9)●	mean	2.0443	14.2951	0.5441	0.2672
		sd	0.1560	0.8126	0.0740	0.0771
175	5 (10)	mean	2.5109	*16.1700	0.6776	0.3922
		sd	0.1383	1.5030	0.0627	0.0378
600	5 (10)	mean	2.0946	*16.0159	0.4567	0.2438
		sd	0.1782	1.4949	0.0367	0.0597

● = n = 8 for ovary weight
* = significantly different from control group $p<0.05$
( ) = number of animals used to calculate mean/sd bodyweights and reproductive organ weights

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 36 (continued) Absolute Organ Weights for Females - Group Mean Values

Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Bodyweight (g) at Terminal Kill	Organ Weight (g)			
				Adrenals	Brain	Ovaries	Heart
0 (Control)	5	mean	286	0.0649	1.8433	0.1316	1.0787
		sd	20	0.0080	0.0554	0.0265	0.1767
600	5	mean	272	0.0618	1.8536	0.1299	1.2679
		sd	15	0.0117	0.1499	0.0234	0.3533

Dose Level (mg/kg/day)	Number of Animals		Organ Weight (g)			
			Kidneys	Liver	Spleen	Thymus
0 (Control)	5	mean	2.0569	10.1392	0.5973	0.3819
		sd	0.2311	1.1763	0.0557	0.1132
600	5	mean	2.1739	11.0586	0.5669	0.4007
		sd	0.1772	1.0548	0.0908	0.0618

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 37 Relative Organ Weights (% of Bodyweight) for Males - Group Mean Values

Non-Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)			
				Adrenals	Brain	Epididymides	Heart
0 (Control)	5 (10)	mean	481	0.0132	0.4586	0.2926	0.3652
		sd	48	0.0017	0.0399	0.0359	0.0416
50	5 (10)	mean	478	0.0125	0.4480	0.2760	0.3620
		sd	42	0.0012	0.0387	0.0303	0.0675
175	5 (10)	mean	493	0.0133	0.4313	0.2697	0.3255
		sd	39	0.0026	0.0418	0.0282	0.0287
600	5 (10)▲	mean	420	0.0132	0.4959	0.2941	0.3632
		sd	39	0.0018	0.0460	0.0402	0.0461

Dose Level (mg/kg/day)	Number of Animals		Relative Organ Weight (%)				
			Kidneys	Liver	Spleen	Testes	Thymus
0 (Control)	5 (10)	mean	0.7828	3.5166	0.1640	0.7431	0.0898
		sd	0.0423	0.3609	0.0221	0.0745	0.0179
50	5 (10)	mean	0.7790	3.3951	0.1623	0.7346	0.0807
		sd	0.0489	0.1419	0.0143	0.0890	0.0159
175	5 (10)	mean	0.8372	3.9071	0.1580	0.7452	0.0796
		sd	0.0893	0.1413	0.0231	0.0540	0.0154
600	5 (10)	mean	0.8273	***4.3039	0.1585	0.8074	0.0848
		sd	0.0503	0.2804	0.0196	0.0941	0.0099

( ) = number of animals used to calculate mean/sd bodyweights and reproductive organ weights
*** = significantly different from control group $p<0.001$
▲ = n=4 for adrenals

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 37 (continued) Relative Organ Weights (% of Bodyweight) for Males - Group Mean Values

Recovery Males

Dose Level (mg/kg/day)	Number of Animals		Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)			
				Adrenals	Brain	Epididymides	Heart
0 (Control)	5	mean	528	0.0114	0.4062	0.2757	0.3430
		sd	68	0.0022	0.0376	0.0250	0.0463
600	5	mean	466	0.0140	0.4405	0.2879	0.3423
		sd	44	0.0016	0.0304	0.0135	0.0338

Dose Level (mg/kg/day)	Number of Animals		Relative Organ Weight (%)				
			Kidneys	Liver	Spleen	Testes	Thymus
0 (Control)	5	mean	0.7120	3.2649	0.1655	0.6931	0.0705
		sd	0.0335	0.1382	0.0066	0.1050	0.0149
600	5	mean	0.7868	**3.8160	0.1604	0.7812	0.0770
		sd	0.0642	0.2658	0.0127	0.0267	0.0066

** = significantly different from control group $p<0.01$

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 38 Relative Organ Weights (% of Bodyweight) for Females - Group Mean Values

Non-Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)			
				Adrenals	Brain	Ovaries	Heart
0 (Control)	5 (9)	mean	319	0.0274	0.5906	0.0423	0.3490
		sd	23	0.0048	0.0505	0.0094	0.0385
50	5 (9)●	mean	314	0.0238	0.5956	0.0414	0.3371
		sd	19	0.0042	0.0321	0.0051	0.0124
175	5 (10)	mean	326	0.0280	0.5753	0.0389	0.3282
		sd	21	0.0031	0.0372	0.0040	0.0190
600	5 (10)	mean	298	0.0226	0.5889	0.0453	0.3298
		sd	8	0.0034	0.0513	0.0160	0.0333

Dose Level (mg/kg/day)	Number of Animals		Relative Organ Weight (%)			
			Kidneys	Liver	Spleen	Thymus
0 (Control)	5 (9)	mean	0.6771	4.3870	0.1920	0.1140
		sd	0.0524	0.2804	0.0092	0.0189
50	5 (9)●	mean	0.6367	4.4541	0.1698	0.0832
		sd	0.0403	0.2148	0.0246	0.0237
175	5 (10)	mean	0.7469	4.7930	0.2014	0.1161
		sd	0.0664	0.3187	0.0207	0.0068
600	5 (10)	mean	0.7050	*5.3937	0.1539	0.0823
		sd	0.0417	0.4259	0.0129	0.0206

● = n = 8 for ovary weight
* = significantly different from control group $p<0.05$
( ) = number of animals used to calculate mean/sd bodyweights and reproductive organ weights

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 38 (continued) **Relative Organ Weights (% of Bodyweight) for Females - Group Mean Values**

Recovery Females

Dose Level (mg/kg/day)	Number of Animals		Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)			
				Adrenals	Brain	Ovaries	Heart
0 (Control)	5	mean	286	0.0229	0.6475	0.0463	0.3768
		sd	20	0.0043	0.0388	0.0095	0.0460
600	5	mean	272	0.0227	0.6814	0.0481	0.4638
		sd	15	0.0040	0.0390	0.0106	0.1136

Dose Level (mg/kg/day)	Number of Animals		Relative Organ Weight (%)			
			Kidneys	Liver	Spleen	Thymus
0 (Control)	5	mean	0.7194	3.5444	0.2094	0.1334
		sd	0.0552	0.2385	0.0172	0.0385
600	5	mean	0.7999	*4.0698	0.2082	0.1479
		sd	0.0586	0.3716	0.0291	0.0265

* = significantly different from control group $p<0.05$

Table 39 Histopathological Findings for Males - Summary Incidence

Terminal Kill

Histopathological Finding	Dose Level (mg/kg/day)					
	0 (Control)	50	175	600	0 (Control) Recovery	600 Recovery
Number of animals examined at terminal kill	5 (10)	5	5	5 (10)	5	5
	Adrenals					
Cortical vacuolation						
no data	5	5	5	5	5	5
absent	4	0	0	4	0	0
(minimal)	1	0	0	1	0	0
	Bone marrow					
Adipose infiltration						
no data	5	5	5	5	5	5
(minimal)	1	0	0	1	0	0
(slight)	2	0	0	3	0	0
(moderate)	2	0	0	1	0	0
	Heart					
Focal myocarditis						
no data	5	5	5	5	5	5
absent	2	0	0	4	0	0
(minimal)	3	0	0	1	0	0
	Kidneys					
Groups of basophilic tubules						
no data	5	5	5	5	5	5
absent	3	0	0	2	0	0
(minimal)	2	0	0	2	0	0
(slight)	0	0	0	1	0	0
Globular accumulations of eosinophilic material						
no data	5	5	5	5	5	5
absent	5	0	0	3	0	0
(minimal)	0	0	0	2	0	0
	Liver					
Mononuclear cell foci						
no data	5	0	0	5	0	0
absent	0	0	0	0	0	1
(minimal)	5	5	5	5	5	4

( ) = number of animals used for examination of reproductive tissues

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 39 (continued) Histopathological Findings for Males - Summary Incidence

Terminal kill

Histopathological Finding	Dose Level (mg/kg/day)					
	0 (Control)	50	175	600	0 (Control) Recovery	600 Recovery
Number of animals examined at terminal kill	5 (10)	5	5	5 (10)	5	5
	Liver					
Centrilobular hepatocytes enlargement						
no data	5	0	0	5	0	0
absent	5	5	5	5	5	4
(minimal)	0	0	0	0	0	1
	Lungs					
Perivascular/peribronchiolar lymphoid aggregations						
no data	5	5	5	5	5	5
(minimal)	5	0	0	5	0	0
Groups of alveolar macrophages						
no data	5	5	5	5	5	5
absent	5	0	0	4	0	0
(minimal)	0	0	0	1	0	0
	Mesenteric lymph node					
Vacuolation histiocytes						
no data	5	5	5	5	5	5
absent	5	0	0	4	0	0
(moderate)	0	0	0	1	0	0
	Oesophagus					
Inflammatory cells peripheral musculature						
no data	5	0	0	5	0	0
absent	5	3	4	4	4	4
present	0	2	1	1	1	1
	Pancreas					
Exocrine atrophy						
no data	5	5	5	5	5	5
absent	4	0	0	5	0	0
(slight)	1	0	0	0	0	0

( ) = number of animals used for examination of reproductive tissues

Table 39 (continued) Histopathological Findings for Males - Summary Incidence

Terminal kill

Histopathological Finding	Dose Level (mg/kg/day)					
	0 (Control)	50	175	600	0 (Control) Recovery	600 Recovery
Number of animals examined at terminal kill	5 (10)	5	5	5 (10)	5	5
	Pituitary					
Vacuolation pars anterior cells						
no data	0	5	5	0	5	5
(minimal)	8	0	0	8	0	0
(slight)	2	0	0	2	0	0
	Prostate					
Epithelial and subepithelial inflammatory cells						
no data	0	5	5	0	5	5
absent	9	0	0	7	0	0
(minimal)	1	0	0	1	0	0
(slight)	0	0	0	2	0	0
	Spleen					
Extramedullary haemopoiesis						
no data	5	5	5	5	5	5
(minimal)	5	0	0	5	0	0
	Testes					
Atrophy gonad 1						
no data	0	5	5	0	5	5
absent	10	0	0	9	0	0
(minimal)	0	0	0	1	0	0
	Thyroids					
Follicular cell hypertrophy						
no data	5	0	0	5	0	0
absent	3	0	2	4	4	2
(minimal)	2	4	3	1	1	3
(slight)	0	1	0	0	0	0
	Statistical Information					
Mode of death						
Terminal kill	10	5	5	10	5	5

( ) = number of animals used for examination of reproductive tissues

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 40 Histopathological Findings for Females - Summary Incidence

Interim Death

Histopathological Finding	Dose Level (mg/kg/day)					
	0 (Control)	50	175	600	0 (Control) Recovery	600 Recovery
Number of animals killed *in extremis*	1	N/A	N/A	N/A	N/A	N/A
	Bone Marrow					
Adipose infiltration (minimal)	1	N/A	N/A	N/A	N/A	N/A
	Caecum					
Submucosal oedema present	1	N/A	N/A	N/A	N/A	N/A
	Heart					
Focal myocarditis (minimal)	1	N/A	N/A	N/A	N/A	N/A
	Liver					
Hepatocyte basophilia present	1	N/A	N/A	N/A	N/A	N/A
	Lungs					
Perivascular/peribronchiolar lymphoid aggregations (minimal)	1	N/A	N/A	N/A	N/A	N/A
	Mammary gland					
Glandular hyperplasia present	1	N/A	N/A	N/A	N/A	N/A
	Spleen					
Extramedullary haemopoiesis (minimal)	1	N/A	N/A	N/A	N/A	N/A
	Thymus					
Atrophy (severe)	1	N/A	N/A	N/A	N/A	N/A
	Urinary bladder					
Peripheral oedema present	1	N/A	N/A	N/A	N/A	N/A
	Uterus/Cervix					
Dilatation horn1 (moderate)	1	N/A	N/A	N/A	N/A	N/A
Dilatation horn2 (moderate)	1	N/A	N/A	N/A	N/A	N/A
Peripheral oedema and inflammatory cells present	1	N/A	N/A	N/A	N/A	N/A

N/A = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 40 (continued) Histopathological Findings for Females - Summary Incidence

Terminal kill

Histopathological Finding	Dose Level (mg/kg/day)					
	0 (Control)	50	175	600	0 (Control) Recovery	600 Recovery
Number of animals examined at terminal kill	5 (9)	5	5	5 (10)	5	5
	Bone marrow					
Adipose infiltration						
no data	4	5	5	5	5	5
(minimal)	3	0	0	2	0	0
(slight)	2	0	0	2	0	0
(moderate)	0	0	0	1	0	0
	Duodenum					
Mucosal hypertrophy						
no data	4	5	5	5	5	5
absent	5	0	0	4	0	0
present	0	0	0	1	0	0
	Heart					
Focal myocarditis						
no data	4	5	5	5	5	5
absent	4	0	0	5	0	0
(minimal)	1	0	0	0	0	0
	Kidneys					
Groups of basophilic tubules						
no data	4	5	5	5	5	5
absent	4	0	0	3	0	0
(minimal)	1	0	0	2	0	0
	Liver					
Mononuclear cell foci						
no data	4	0	0	5	0	0
absent	4	0	0	1	1	1
(minimal)	1	5	5	4	4	4
Centrilobular hepatocyte enlargement						
no data	4	0	0	5	0	0
absent	5	5	5	2	5	5
(minimal)	0	0	0	3	0	0

( ) = number of animals used for examination of reproductive tissues

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 40 (continued) Histopathological Findings for Females - Summary Incidence

Terminal kill

Histopathological Finding	Dose Level (mg/kg/day)					
	0 (Control)	50	175	600	0 (Control) Recovery	600 Recovery
Number of animals examined at terminal kill	5 (9)	5	5	5 (10)	5	5
	Liver					
Generalised hepatocyte enlargement						
no data	4	0	0	5	0	0
absent	4	4	3	5	5	5
(minimal)	1	1	1	0	0	0
(slight)	0	0	1	0	0	0
Focal hepatocyte necrosis						
no data	4	0	0	5	0	0
absent	5	4	5	5	5	5
(minimal)	0	1	0	0	0	0
	Lungs					
Perivascular/peribronchiolar lymphoid aggregations						
no data	4	5	5	5	5	5
(minimal)	5	0	0	5	0	0
Focal pneumonitis						
no data	4	5	5	5	5	5
absent	4	0	0	5	0	0
(minimal)	1	0	0	0	0	0
Groups of alveolar macrophages						
no data	4	5	5	5	5	5
absent	3	0	0	3	0	0
(minimal)	2	0	0	2	0	0
	Mammary gland					
Glandular hyperplasia						
no data	4	5	5	5	5	5
present	5	0	0	5	0	0

( ) = number of animals used for examination of reproductive tissues

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 40 (continued) Summary Incidence of Histopathological Findings

Terminal kill

Histopathological Finding	Dose Level (mg/kg/day)					
	0 (Control)	50	175	600	0 (Control) Recovery	600 Recovery
Number of animals examined at terminal kill	5 (9)	5	5	5 (10)	5	5
	Oesophagus					
Inflammatory cells peripheral musculature						
no data	4	0	0	5	0	0
absent	5	5	1	1	5	4
present	0	0	4	4	0	1
	Pancreas					
Exocrine atrophy						
no data	4	5	5	5	5	5
absent	4	0	0	5	0	0
(minimal)	1	0	0	0	0	0
	Skeletal muscle					
Mononuclear cell foci						
no data	4	5	5	5	5	5
absent	4	0	0	5	0	0
(minimal)	1	0	0	0	0	0
	Spleen					
Extramedullary haemopoiesis						
no data	4	5	5	5	5	5
(minimal)	4	0	0	5	0	0
(slight)	1	0	0	0	0	0
	Thyroids					
Follicular cell hypertrophy						
no data	4	0	0	5	0	0
absent	5	4	3	1	5	4
(minimal)	0	1	2	3	0	1
(slight)	0	0	0	1	0	0
	Uterus/Cervix					
Peripheral foam cells/ haemorrhage/pigment						
no data	0	5	5	0	5	5
absent	1	0	0	0	0	0
present	8	0	0	10	0	0
	Statistical Information					
Mode of death						
Interim death	1	0	0	0	0	0
Terminal kill	9	5	5	10	5	5

( ) = number of animals used for examination of reproductive tissues

FIGURES

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Figure 1 Group Mean Bodyweights - Males

Non-Recovery Males

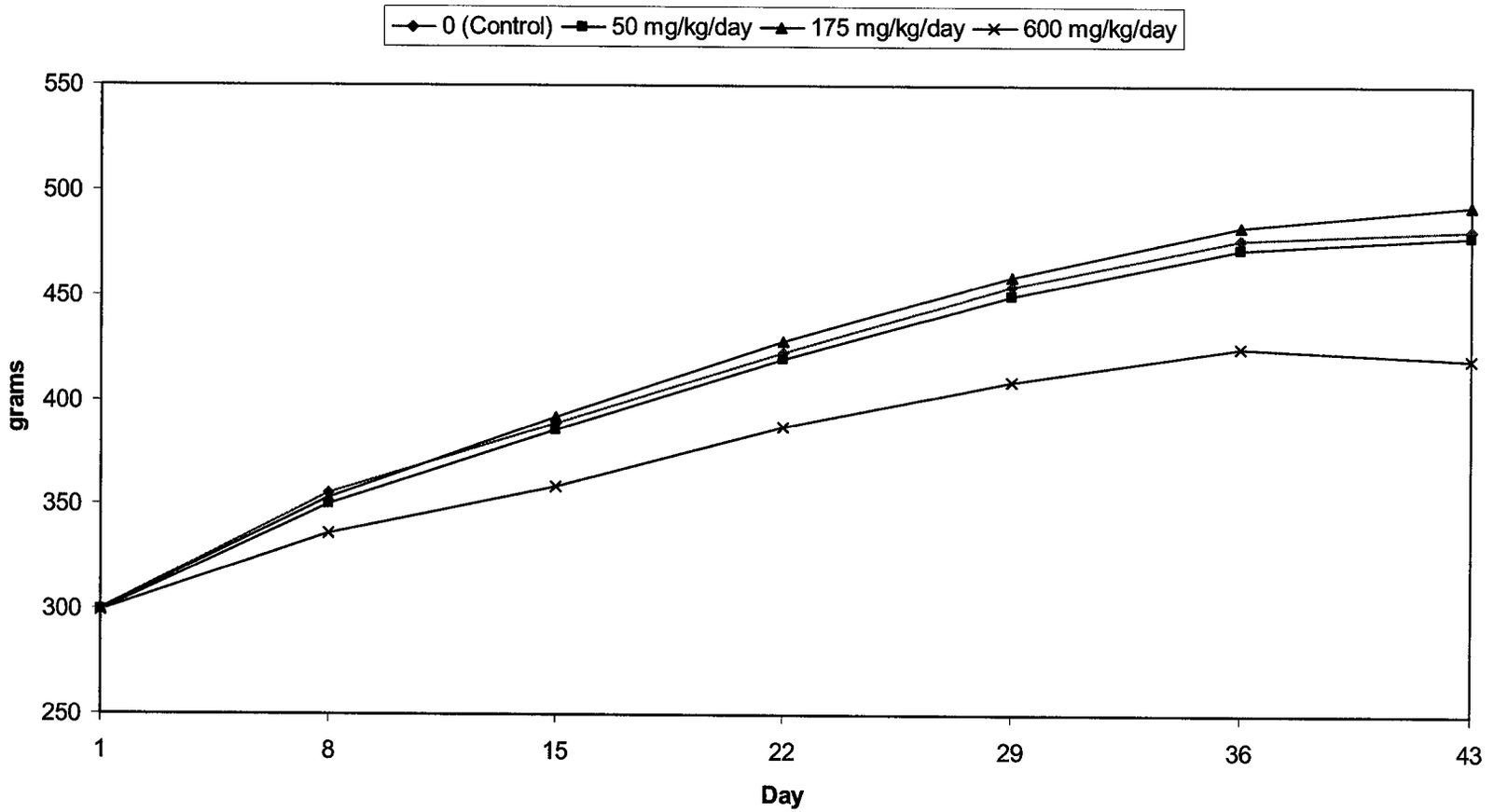
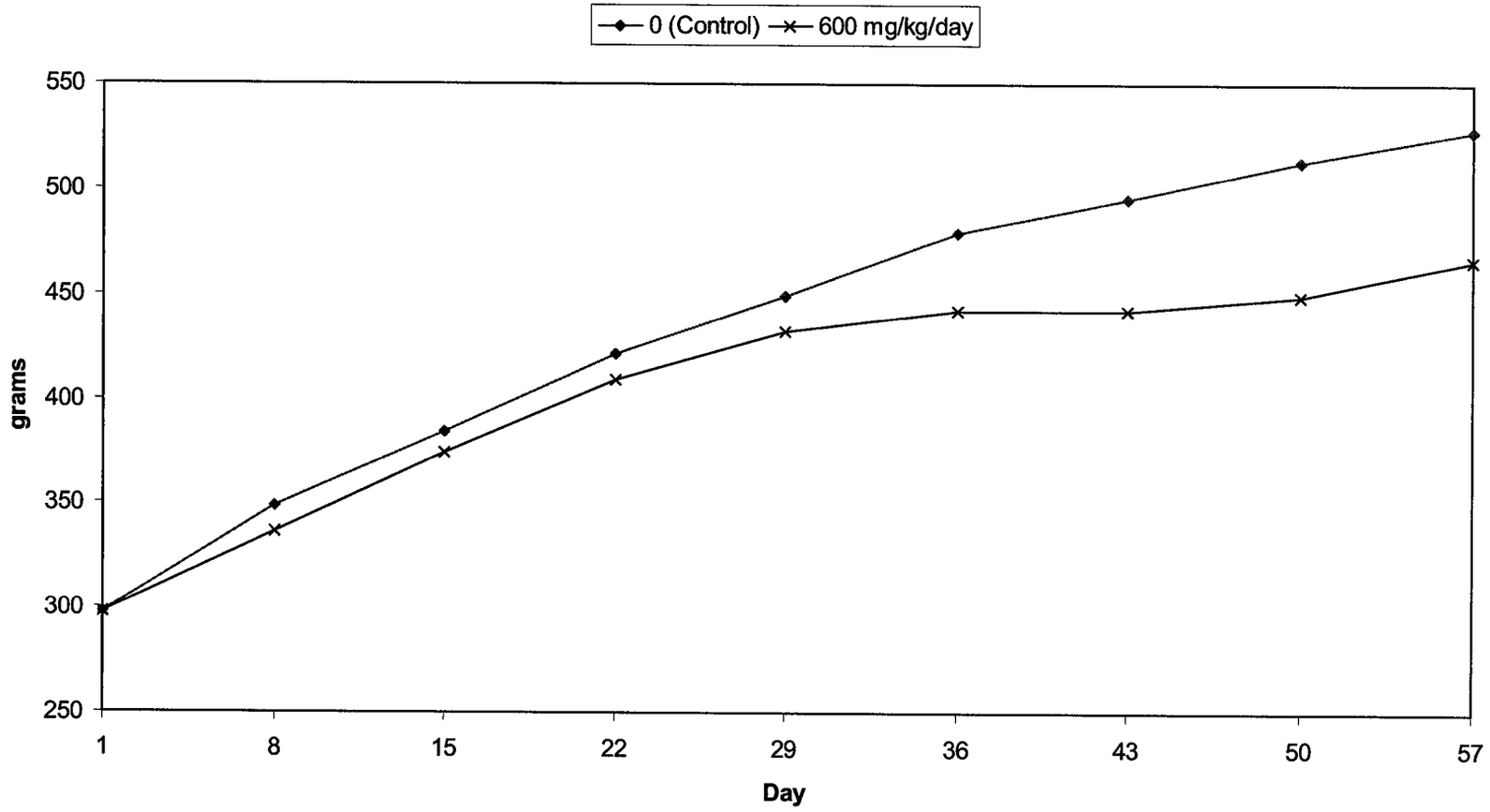


Figure 1 (continued) **Group Mean Bodyweights - Males**

Recovery Males



1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Figure 2 Group Mean Bodyweights - Females

Non-Recovery Females
Maturation

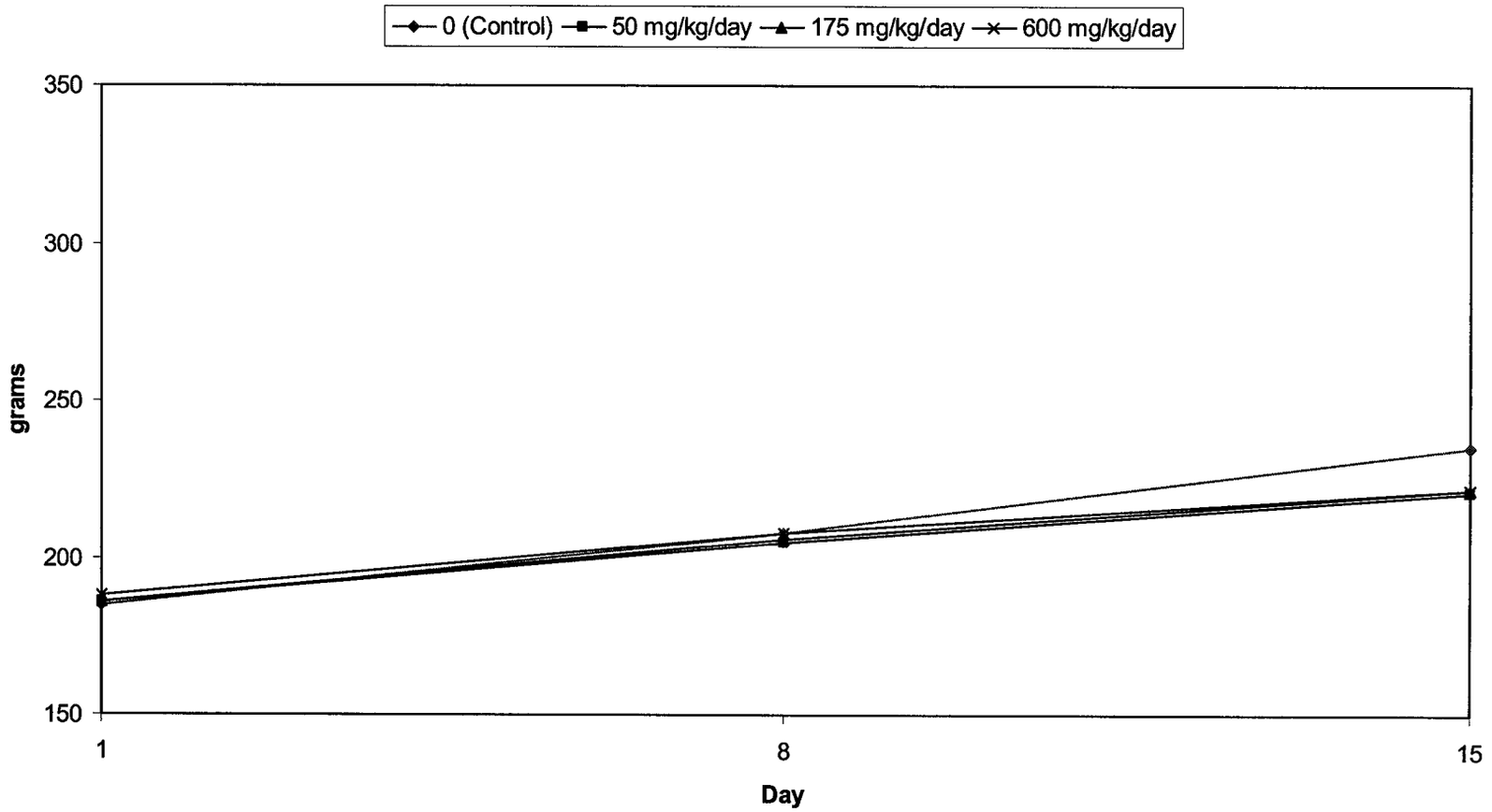
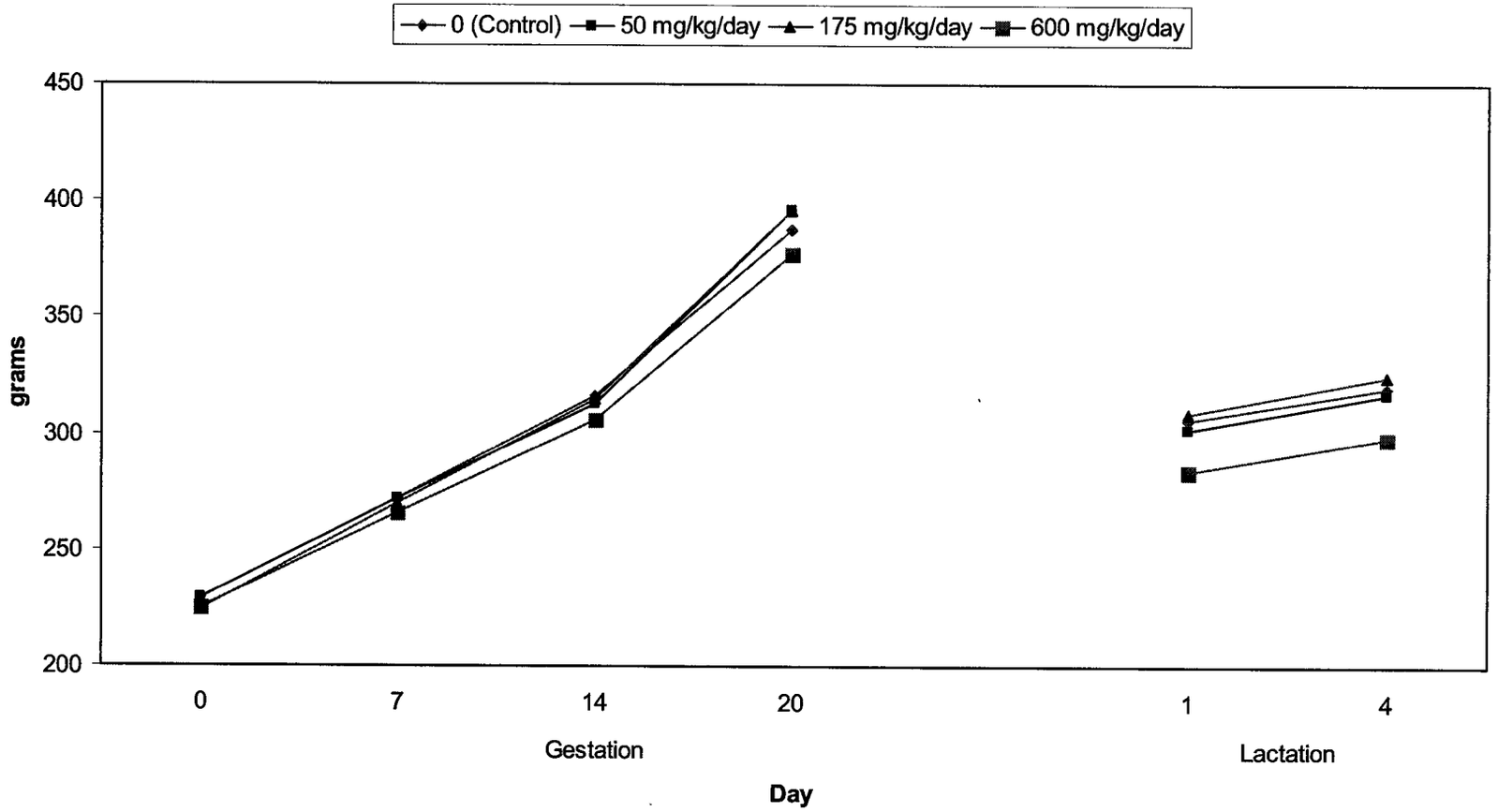


Figure 2 (continued) **Group Mean Bodyweights – Females**

Non-Recovery Females
Gestation and Lactation



1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Figure 2 (continued) **Group Mean Bodyweights – Females**

Recovery Females

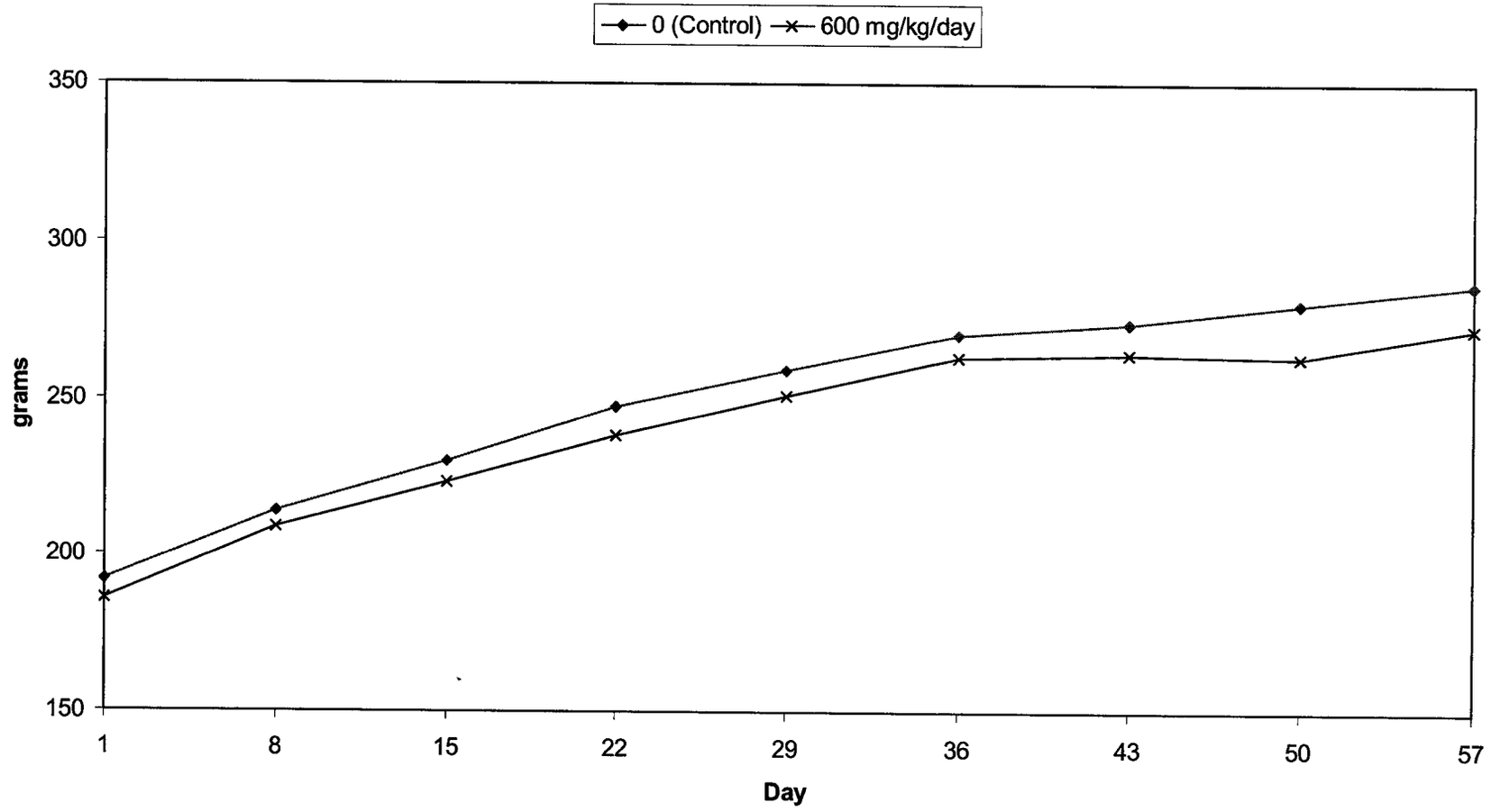
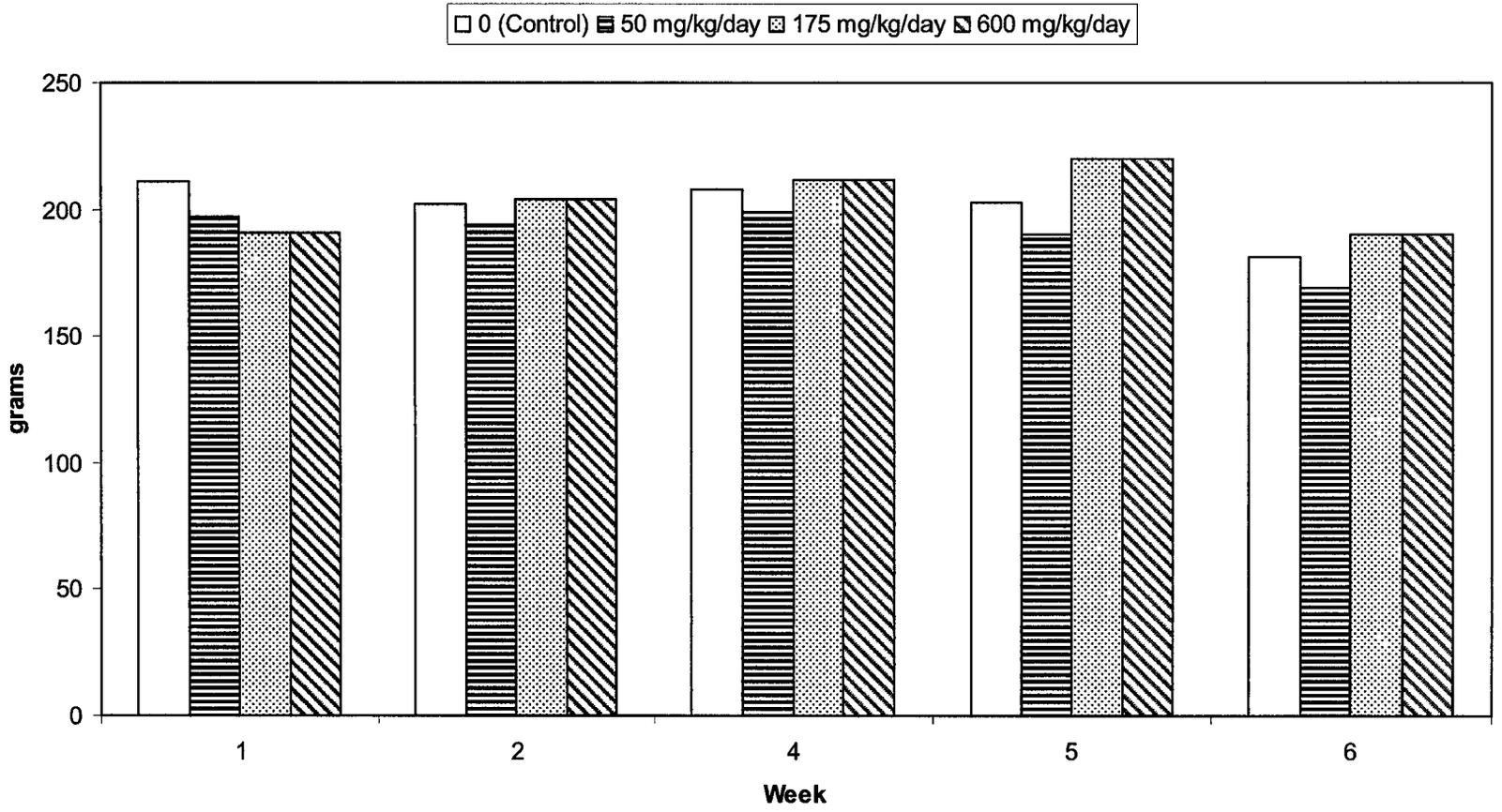


Figure 3 Group Mean Food Consumption - Males

Non-Recovery Males



1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Figure 3 (continued) Group Mean Food Consumption - Males

Recovery Males

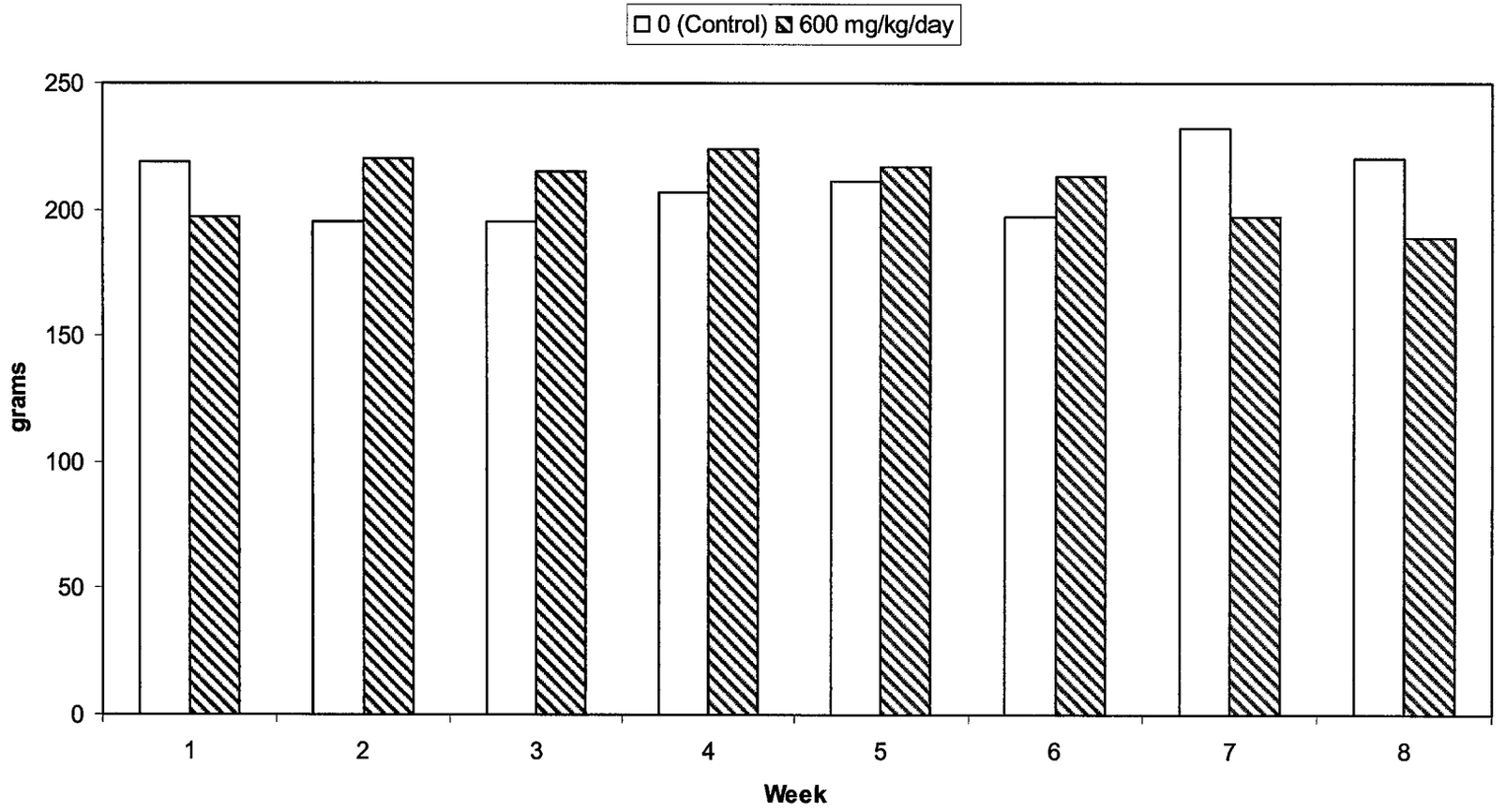
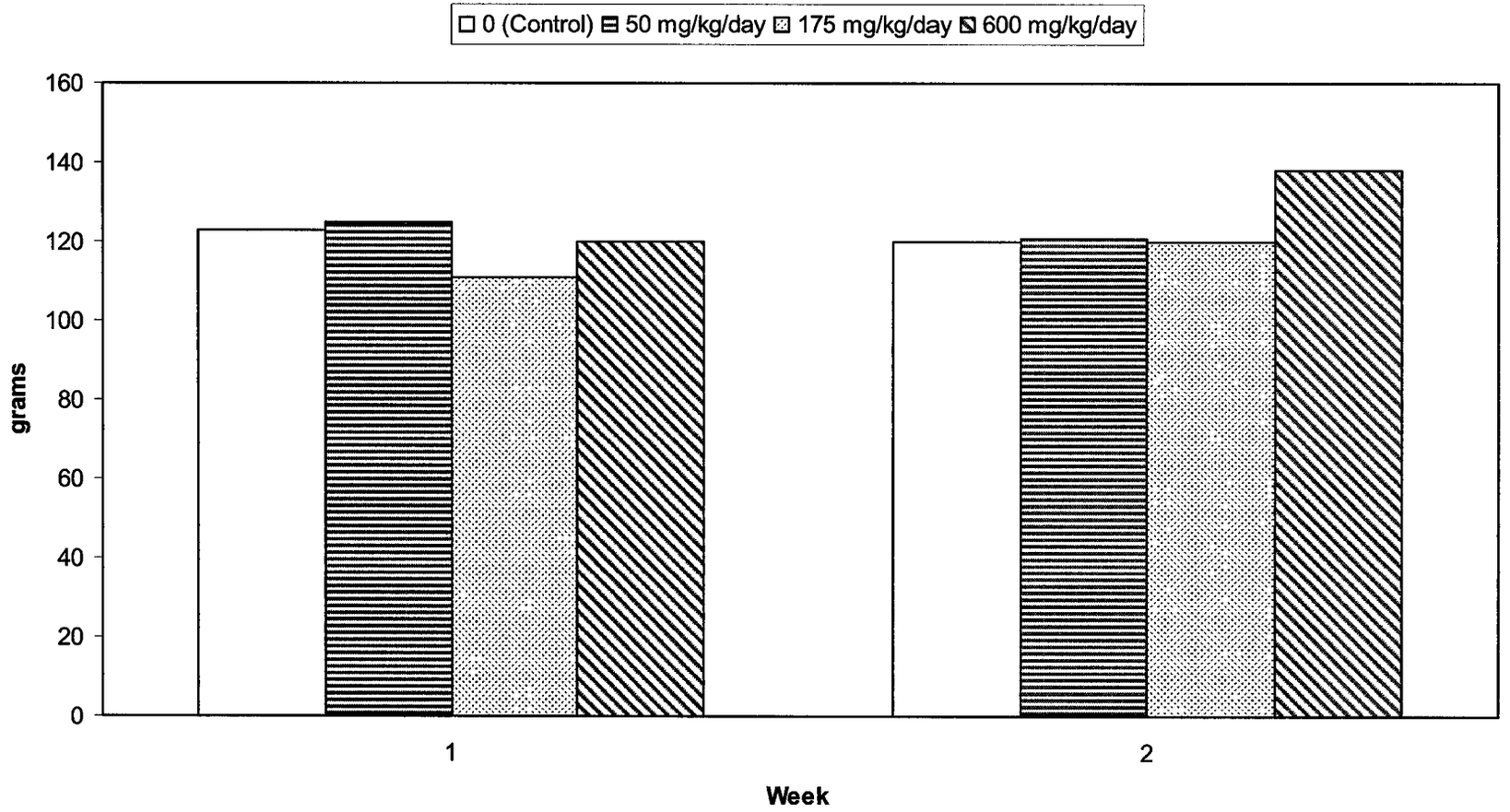


Figure 4 Group Mean Food Consumption - Females

Non-Recovery Females
Maturation



1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Figure 4 (continued) Group Mean Food Consumption – Females

Non-Recovery Females
Gestation and Lactation

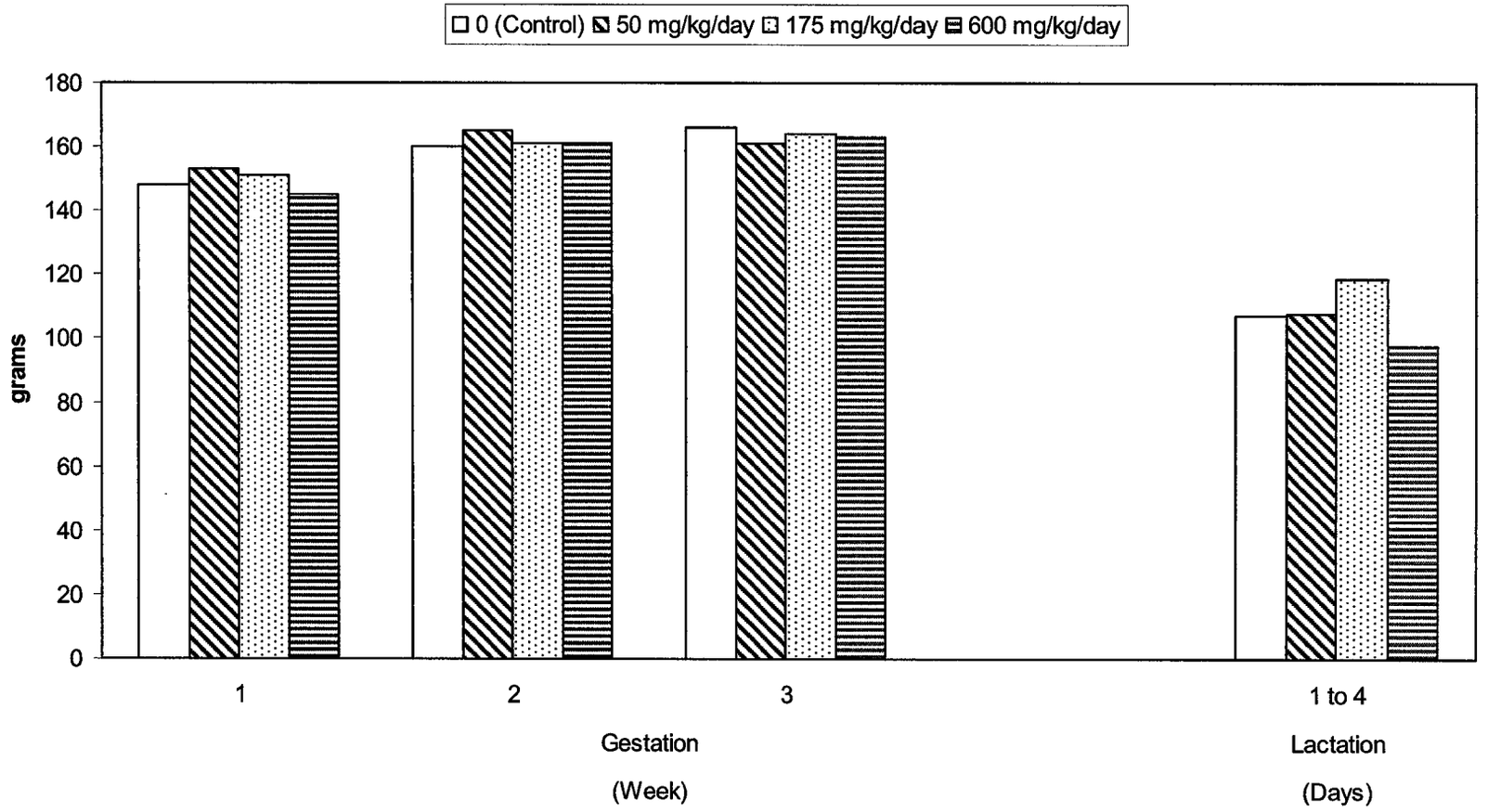
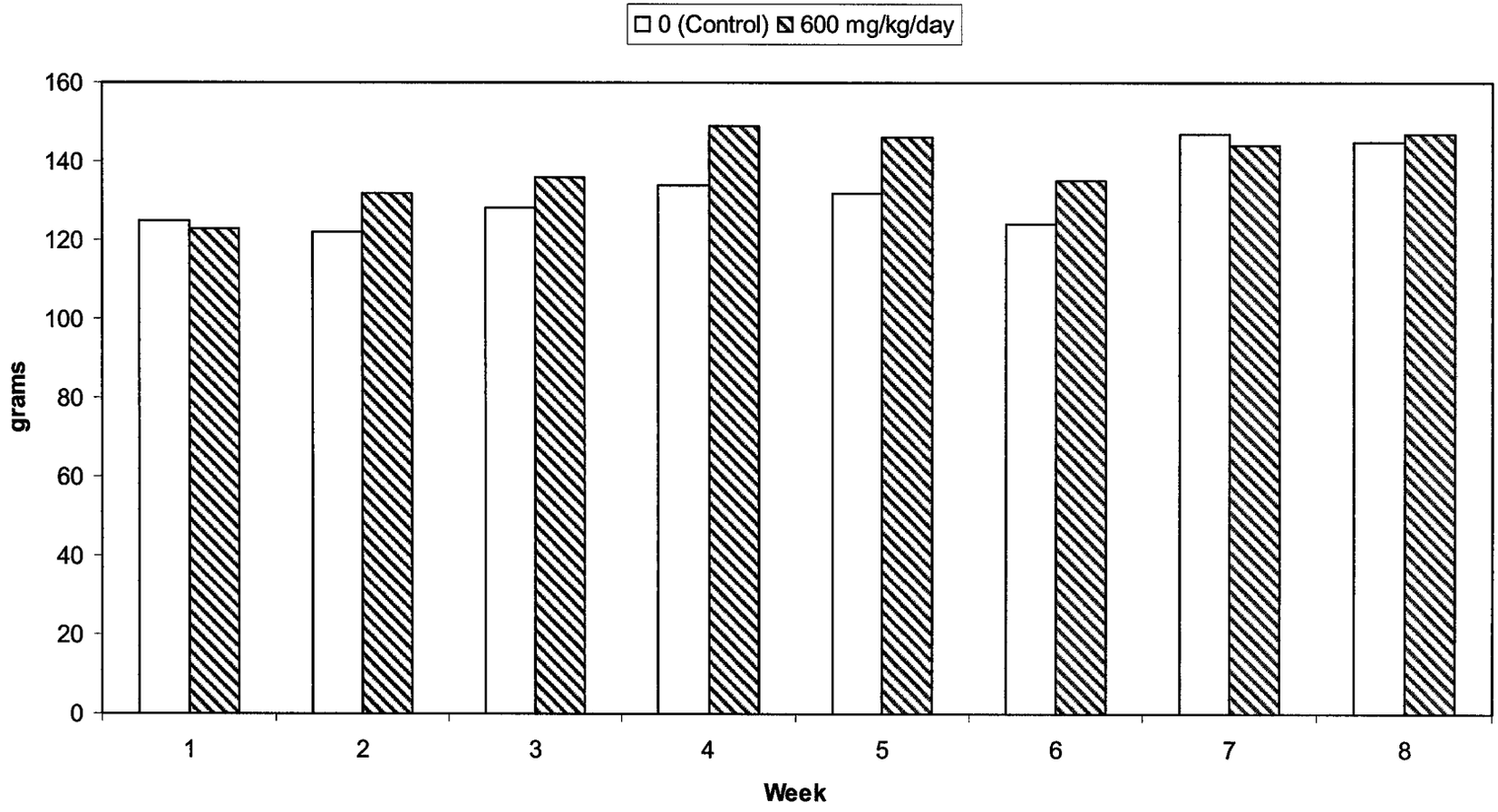


Figure 4 (continued) **Group Mean Food Consumption – Females**

Recovery Females



APPENDICES

Appendix 1 Scoring System and Explanation for Behavioural Assessments and Sensory Reactivity Tests

1. NEUROLOGIC

These parameters are the first to be evaluated when the animal is placed in the arena:

1.1 Transfer Arousal (Time to Movement) and Locomotion

-2 = animal stays in one place
-1 = slow, deliberate movement
0 = moderate, undisturbed investigation of environment
1 = active progression around arena
2 = darting movements

1.2 Tail Elevation

0 = flattened
1 = rigidly horizontally extended
2 = rigidly diagonally elevated
3 = rigidly vertical
4 = diagonally retrograde (past vertical)

2. GAIT AND CO-ORDINATION

Tiptoe (Wt)	Hindlimbs raised on tiptoe during movement
High stepping (Wh)	Forelimbs lifted high during movement
Spastic (Sp)	Shuffling of limbs
Waddling (W)	Lateral movements
Dysmetric (D)	Unco-ordinated movement with tremors
Splayed (Ws)	Thighs splayed outwards, animal appears crouched
Scissor (Sc)	Forelimbs cross over when extended
Ataxic (A)	Lack of co-ordinated movement of trunk, pelvis and limbs.
	Observation graded: 2 = slight
	4 = moderate (does not fall)
	6 = severe (falls repeatedly)
	8 = cannot stand

When gait appears normal, observation is graded: 0 = normal

Appendix 1 (continued) Scoring System and Explanation for Behavioural Assessments and Sensory Reactivity Tests

3. CNS EXCITATION

3.1 Tremors

These are general involuntary movements of the muscles

Exertion (E)	only occurs during movement
Rest (R)	only occurs when animal is resting
Whole body (W)	
Head only (H)	
Body only (B)	
Tail only (T)	

When present, any observation is also graded:
2 = slight
4 = moderate
6 = severe

When no tremors are detected, observation is graded: 0 = none

A combination of these observations requires more than one code.

3.2 Twitches

Identified as brief, coarse jerks of body or limbs – observation graded:

2 = slight
4 = moderate
6 = severe

3.3 Convulsions

Clonic (C)	Convulsions with alternate contraction and relaxation of muscles
Running excitement (Re)	Often accompanied by clonic convulsions
Champing (Ch)	Clonus of the paws only
Hopping (H)	Animal repeatedly "hops" into the air
Asphyxeal (As)	Terminal convulsion, results in death from respiratory failure

Appendix 1 (continued) Scoring System and Explanation for Behavioural Assessments and Sensory Reactivity Tests

Tonic (Ct)	Seizure in which the head, body and limbs are arched backwards
Emprosthotonus (Em)	Seizure where the head, body and limbs are arched forwards

When no convulsions are detected, observation is graded: 0 = none

3.4 Bizarre Behaviour

Any bizarre behaviour is recorded using a unique code.

When behaviour appears normal, observation is graded: 0 = normal

4. AUTONOMIC

Salivation*	Excessive visible wetness around the mouth
Pilo-erection*	Fur stands up – marked cases are described as "puff ball" appearance
Exophthalmia	Bulging eyes
Lachrymation	Tear staining (clear fluid) Chromodacryorrhea (red/pink fluid)
Hyperthermia (He)	
Hypothermia (Ho)	

If neither hyper or hypothermia is detected, observation is graded: 0 = absent

Skin colour**	Blue (cyanotic) Redness of extremities Skin pallor
Respiration	Decreased respiratory rate Gasping Increased rate Laboured Noisy

When respiration appears normal, observation is graded: 0 = normal

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* When present, observation is graded: 2 = slight, 4 = severe. If absent, observation is graded: 0 = absent

** When present, observation is graded: 2 = slight, 4 = moderate, 6 = severe. If absent, observation is graded: 0 = normal

Appendix 1 (continued) Scoring System and Explanation for Behavioural Assessments and Sensory Reactivity Tests

Palpebral closure	Degree of eyelid closure eg ptosis – observation is graded: normal slight moderate severe
Urination and defecation	During the study this can only be observed as urogenital wetness and/or diarrhoea. In the open arena, the number of occasions that the animal defecates/urinates is recorded

5. MANIPULATIVE TESTS

Performed in the open arena:

5.1 Grasp Response

The animal is grasped around the body and its reaction is scored:

0 = no response
1 = animal struggles slightly but becomes passive
2 = animal repeatedly struggles with/without vocalisation
3 = animal struggles violently with/without vocalisation
4 = animal attempts to bite operator

5.2 Vocalisation

The number of vocalisations exhibited by the animal during assessment.

5.3 Toe Pinch

On handling one toe of a hindfoot is lightly pressed with a pair of forceps:

-3 = no response
-2 = animal shows awareness of actions
-1 = withdrawal
0 = rapid withdrawal with single vocalisation
1 = rapid withdrawal with multiple vocalisations

Appendix 1 (continued) Scoring System and Explanation for Behavioural Assessments and Sensory Reactivity Tests

5.4 Tail Pinch

Whilst animal is in the arena, the end of the tail is lightly pressed with forceps:

-2 = no response
-1 = animal freezes/shows awareness of grasping
0 = animal attempts to escape/struggles with none or single vocalisation
1 = animal struggles violently with multiple vocalisations

5.5 Finger Approach

Whilst animal is in the arena the operator moves one finger towards the animal:

-1 = animal is oblivious to approach
0 = animal is aware of finger but is unmoved
1 = head sways from side to side
2 = moves towards finger
3 = investigates finger by moving onto it

5.6 Touch Escape

Whilst animal is in the arena the operator runs his finger down the body of the animal:

-2 = no response
-1 = animal twitches ears, investigates finger
0 = animal crouches
1 = animal moves away but is unhurried
2 = animal moves away as if startled

5.7 Pupil Reflex

The animal is placed in a darkened area to allow the pupils to dilate. A light beam is shone into each eye separately and the pupil is observed for immediate constriction.

Appendix 1 (continued) Scoring System and Explanation for Behavioural Assessments and Sensory Reactivity Tests

The response recorded:

-2 = no response
-1 = sluggish
0 = normal

5.8 Blink Reflex (Palpebral Closure)

The operator attempts to touch the eye of the rat, the response is recorded:

-2 = no response
-1 = sluggish
0 = normal blink reflex
1 = rapid or repeated eye blink

5.9 Startle Reflex

A sharp sudden noise is produced by a noise generator or finger snap or similar. Each animal is held lightly but firmly facing the origin of the noise. The response is recorded:

-1 = no response
0 = normal
1 = hyper-responsive

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 2 Functional Performance - Individual Values

DOSE LEVEL: 0 (Control)

Animal Number and Sex	Grip Strength (g)						Motor Activity			
	Forelimb			Hindlimb			Overall		Final 20% of Trial	
	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	% Activity	% Mobile Activity	% Activity	% Mobile Activity
1 M	541	1128	593	275	456	210	15.4	0.0	4.7	0.0
2 M	942	968	705	562	636	603	35.5	0.1	0.0	0.0
3 M	592	1053	1426	339	323	346	38.5	0.0	11.7	0.0
4 M	917	600	446	343	344	390	9.0	0.0	2.5	0.0
5 M	795	725	500	459	424	242	50.4	0.2	47.2	0.3
mean			795			397	29.8	0.0	13.2	0.1
sd			274			127	17.1	0.1	19.5	0.1

M = male

Appendix 2 (continued) Functional Performance - Individual Values

DOSE LEVEL: 0 (Control)

Animal Number and Sex	Grip Strength (g)						Motor Activity			
	Forelimb			Hindlimb			Overall		Final 20% of Trial	
	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	% Activity	% Mobile Activity	% Activity	% Mobile Activity
11 F	741	711	383	187	222	246	21.4	0.1	3.3	0.0
12 F	987	976	1203	292	178	458	24.9	0.1	0.0	0.0
13 F	1064	909	1000	232	279	200	8.7	0.0	0.0	0.0
14 F	1318	947	1098	329	221	251	13.2	0.1	0.0	0.0
16 F	1103	642	1032	413	232	252	15.4	0.0	1.1	0.0
mean			941			266	16.7	0.1	0.9	0.0
sd			237			80	6.5	0.1	1.4	0.0

F = female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 2 (continued) Functional Performance - Individual Values

DOSE LEVEL: 50 mg/kg/day

Animal Number and Sex	Grip Strength (g)						Motor Activity			
	Forelimb			Hindlimb			Overall		Final 20% of Trial	
	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	% Activity	% Mobile Activity	% Activity	% Mobile Activity
21 M	532	1420	665	268	151	288	2.2	0.0	0.6	0.0
22 M	1129	889	1032	499	656	206	19.2	0.0	0.0	0.0
23 M	515	964	1387	283	192	269	10.6	0.0	0.0	0.0
24 M	913	664	1299	589	610	265	33.7	0.0	29.2	0.0
26 M	1126	642	625	492	448	504	35.5	0.0	0.8	0.0
mean			920			381	20.2	0.0	6.1	0.0
sd			307			168	14.4	0.0	12.9	0.0

M = male

Appendix 2 (continued) Functional Performance - Individual Values

DOSE LEVEL: 50 mg/kg/day

Animal Number and Sex	Grip Strength (g)						Motor Activity			
	Forelimb			Hindlimb			Overall		Final 20% of Trial	
	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	% Activity	% Mobile Activity	% Activity	% Mobile Activity
31 F	1054	1197	1079	183	191	117	3.4	0.0	1.7	0.0
32 F	1127	806	962	239	341	249	15.8	0.2	0.6	0.0
33 F	895	759	537	403	356	378	17.6	0.1	5.0	0.0
34 F	1089	1065	1078	289	223	222	30.3	0.0	3.6	0.0
35 F	1193	1170	925	293	295	182	22.5	0.1	4.7	0.0
mean			996			264	17.9	0.1	3.1	0.0
sd			184			82	9.9	0.1	1.9	0.0

F = female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 2 (continued) Functional Performance - Individual Values

DOSE LEVEL: 175 mg/kg/day

Animal Number and Sex	Grip Strength (g)						Motor Activity			
	Forelimb			Hindlimb			Overall		Final 20% of Trial	
	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	% Activity	% Mobile Activity	% Activity	% Mobile Activity
41 M	671	569	930	437	269	210	27.0	0.0	3.3	0.0
42 M	639	567	1493	291	233	226	22.3	0.0	6.9	0.0
43 M	558	999	880	451	552	271	36.3	0.0	15.0	0.0
44 M	1278	1131	1082	279	315	428	27.6	0.0	20.6	0.0
45 M	719	536	1138	170	278	297	20.1	0.0	0.0	0.0
mean			879			314	26.6	0.0	9.2	0.0
sd			301			106	6.2	0.0	8.5	0.0

M = male

Appendix 2 (continued) Functional Performance - Individual Values

DOSE LEVEL: 175 mg/kg/day

Animal Number and Sex	Grip Strength (g)						Motor Activity			
	Forelimb			Hindlimb			Overall		Final 20% of Trial	
	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	% Activity	% Mobile Activity	% Activity	% Mobile Activity
51 F	490	1067	1103	161	160	192	26.5	0.5	30.6	0.0
52 F	1165	1083	814	210	308	317	20.6	0.1	2.2	0.0
53 F	1132	1171	1114	190	214	406	37.2	0.1	13.9	0.0
54 F	1158	1230	937	267	184	550	46.2	0.0	33.3	0.0
55 F	385	936	921	282	261	286	18.8	0.1	0.0	0.0
mean			980			266	29.9	0.2	16.0	0.0
sd			249			104	11.6	0.2	15.5	0.0

F = female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 2 (continued) Functional Performance - Individual Values

DOSE LEVEL: 600 mg/kg/day

Animal Number and Sex	Grip Strength (g)						Motor Activity			
	Forelimb			Hindlimb			Overall		Final 20% of Trial	
	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	% Activity	% Mobile Activity	% Activity	% Mobile Activity
61 M	1006	599	1212	432	158	576	21.4	0.0	1.7	0.0
62 M	913	1128	533	308	508	150	3.8	0.0	0.0	0.0
63 M	472	997	1123	275	259	278	21.8	0.0	0.8	0.0
64 M	1337	1237	582	342	296	283	24.6	0.0	2.2	0.0
66 M	915	258	765	568	164	164	7.3	0.0	6.7	0.0
mean			872			317	15.8	0.0	2.3	0.0
sd			322			144	9.5	0.0	2.6	0.0

M = male

Appendix 2 (continued) Functional Performance - Individual Values

DOSE LEVEL: 600 mg/kg/day

Animal Number and Sex	Grip Strength (g)						Motor Activity			
	Forelimb			Hindlimb			Overall		Final 20% of Trial	
	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	% Activity	% Mobile Activity	% Activity	% Mobile Activity
71 F	470	506	928	121	163	159	32.7	0.0	0.6	0.0
72 F	1065	928	1118	213	129	211	19.7	0.1	0.0	0.0
73 F	1058	679	1269	229	153	367	22.7	0.2	0.6	0.0
74 F	1072	1051	1219	388	284	353	14.7	0.0	10.6	0.0
75 F	308	923	695	204	426	378	27.6	0.1	1.7	0.0
mean			886			252	23.5	0.1	2.7	0.0
sd			289			105	7.0	0.1	4.5	0.0

F = female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 3 Sensory Reactivity Assessments - Individual Values

DOSE LEVEL: 0 (Control)

Parameter	Animal Number and Sex									
	1 M	2 M	3 M	4 M	5 M	11 F	12 F	13 F	14 F	16 F
Grasp response	0	0	0	0	0	0	0	0	0	0
Vocalisation	0	0	0	0	0	0	0	0	0	0
Toe pinch	0	0	0	0	0	0	0	0	0	0
Tail pinch	0	0	0	0	0	0	0	0	0	0
Finger approach	0	0	0	0	0	0	0	0	0	0
Touch escape	0	0	0	0	0	0	0	0	0	0
Pupil reflex	0	0	0	0	0	0	0	0	0	0
Blink reflex	0	0	0	0	0	0	0	0	0	0
Startle reflex	0	0	0	0	0	-	-	-	-	-

M = male
F = female
- = data unavailable

Appendix 3 (continued) Sensory Reactivity Assessments - Individual Values

DOSE LEVEL: 50 mg/kg/day

Parameter	Animal Number and Sex									
	21 M	22 M	23 M	24 M	25 M	31 F	32 F	33 F	34 F	35 F
Grasp response	0	0	0	0	0	0	0	0	0	0
Vocalisation	0	0	0	0	0	0	0	0	0	1
Toe pinch	0	0	0	0	0	0	0	0	0	0
Tail pinch	0	0	-1	-1	0	0	0	0	0	0
Finger approach	0	0	0	0	0	0	0	0	0	0
Touch escape	0	0	0	0	0	0	0	0	0	0
Pupil reflex	0	0	0	0	0	0	0	0	0	0
Blink reflex	0	0	0	0	0	0	0	0	0	0
Startle reflex	0	0	0	0	0	-	-	-	-	-

M = male
F = female
- = data unavailable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 3 (continued) Sensory Reactivity Assessments - Individual Values

DOSE LEVEL: 175 mg/kg/day

Parameter	Animal Number and Sex									
	41 M	42 M	43 M	44 M	45 M	51 F	52 F	53 F	54 F	55 F
Grasp response	0	0	0	0	0	0	0	0	0	0
Vocalisation	0	0	0	0	0	0	0	0	1	0
Toe pinch	0	0	0	-1	0	0	0	0	0	0
Tail pinch	-1	0	0	-1	0	0	0	0	0	0
Finger approach	0	0	0	0	0	0	0	0	0	0
Touch escape	0	1	0	0	0	1	0	0	1	0
Pupil reflex	0	0	0	0	0	0	0	0	0	0
Blink reflex	0	0	0	0	0	0	0	0	0	0
Startle reflex	0	0	0	0	0	-	-	-	-	-

M = male
F = female
- = data unavailable

Appendix 3 (continued) Sensory Reactivity Assessments - Individual Values

DOSE LEVEL: 600 mg/kg/day

Parameter	Animal Number and Sex									
	61 M	62 M	63 M	64 M	65 M	71 F	72 F	73 F	74 F	75 F
Grasp response	0	0	0	0	0	0	0	0	0	0
Vocalisation	0	0	0	0	0	0	1	0	1	0
Toe pinch	0	0	0	0	0	0	0	0	0	0
Tail pinch	-1	-1	-2	0	0	0	0	0	0	0
Finger approach	0	0	0	0	0	0	0	0	0	0
Touch escape	0	0	1	0	1	0	0	0	0	0
Pupil reflex	0	0	0	0	0	0	0	0	0	0
Blink reflex	0	0	0	0	0	0	0	0	0	0
Startle reflex	0	0	0	0	0	-	-	-	-	-

M = male
F = female
- = data unavailable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 4 Bodyweights and Bodyweight Change for Males - Individual Values

DOSE LEVEL: 0 (Control)

Animal Number	Bodyweight (g) at Day								
	1	8	15 P	22	29	36	43	50	57
1	304	343	379	420	460	487	489	-	-
2	295	356	374	396	420	445	449	-	-
3	307	354	383	406	436	461	457	-	-
4	298	351	369	402	435	466	457	-	-
5	284	323	345	382	400	419	410	-	-
6	308	366	407	448	481	512	528	-	-
7	298	344	366	397	418	430	434	-	-
8	289	361	400	445	473	488	495	-	-
9	288	365	413	451	497	522	533	-	-
10	331	395	450	478	520	544	561	-	-
81	296	342	370	405	427	458	471	485	496
82	279	319	334	364	383	406	410	420	440
83	308	368	378	409	431	459	490	509	512
84	296	368	414	463	494	522	539	568	586
85	311	350	422	462	510	550	567	585	607

Animal Number	Bodyweight Change (g) during Week							
	1	2	3	4	5	6	7	8
1	39	36 *(75)*	41 *(116)*	40 *(156)*	27 *(183)*	2 *(185)*	-	-
2	61	18 *(79)*	22 *(101)*	24 *(125)*	25 *(150)*	4 *(154)*	-	-
3	47	29 *(76)*	23 *(99)*	30 *(129)*	25 *(154)*	-4 *(150)*	-	-
4	53	18 *(71)*	33 *(104)*	33 *(137)*	31 *(168)*	-9 *(159)*	-	-
5	39	22 *(61)*	37 *(98)*	18 *(116)*	19 *(135)*	-9 *(126)*	-	-
6	58	41 *(99)*	41 *(140)*	33 *(173)*	31 *(204)*	16 *(220)*	-	-
7	46	22 *(68)*	31 *(99)*	21 *(120)*	12 *(132)*	4 *(136)*	-	-
8	72	39 *(111)*	45 *(156)*	28 *(184)*	15 *(199)*	7 *(206)*	-	-
9	77	48 *(125)*	38 *(163)*	46 *(209)*	25 *(234)*	11 *(245)*	-	-
10	64	55 *(119)*	28 *(147)*	42 *(189)*	24 *(213)*	17 *(230)*	-	-
81	46	28 *(74)*	35 *(109)*	22 *(131)*	31 *(162)*	13 *(175)*	14 *(189)*	11 *(200)*
82	40	15 *(55)*	30 *(85)*	19 *(104)*	23 *(127)*	4 *(131)*	10 *(141)*	20 *(161)*
83	60	10 *(70)*	31 *(101)*	22 *(123)*	28 *(151)*	31 *(182)*	19 *(201)*	3 *(204)*
84	72	46 *(118)*	49 *(167)*	31 *(198)*	28 *(226)*	17 *(243)*	29 *(272)*	18 *(290)*
85	39	72 *(111)*	40 *(151)*	48 *(199)*	40 *(239)*	17 *(256)*	18 *(274)*	22 *(296)*

P = animals paired for mating
( ) = *cumulative bodyweight change relative to Day 1*
- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 4 (continued) Bodyweights and Bodyweight Change for Males - Individual Values

DOSE LEVEL: 50 mg/kg/day

Animal Number	Bodyweight (g) at Day						
	1	8	15 P	22	29	36	43
21	296	327	349	375	403	417	422
22	283	339	372	415	449	467	450
23	288	322	339	376	393	410	410
24	316	380	418	455	496	529	522
25	300	348	375	406	445	468	472
26	310	368	418	444	467	496	502
27	300	353	406	445	479	504	526
28	278	330	361	394	424	443	461
29	319	375	422	455	483	504	525
30	297	357	402	436	460	484	486

Animal Number	Bodyweight Change (g) during Week					
	1	2	3 P	4	5	6
21	*31*	22 *(53)*	26 *(79)*	28 *(107)*	14 *(121)*	5 *(126)*
22	*56*	*33 (89)*	43 *(132)*	34 *(166)*	18 *(184)*	-17 *(167)*
23	34	17 *(51)*	37 *(88)*	17 *(105)*	17 *(122)*	0 *(122)*
24	64	38 *(102)*	37 *(139)*	41 *(180)*	33 *(213)*	-7 *(206)*
25	*48*	*27(75)*	31 *(106)*	39 *(145)*	23 *(168)*	4 *(172)*
26	58	50 *(108)*	26 *(134)*	23 *(157)*	29 *(186)*	6 *(192)*
27	*53*	53 *(106)*	39 *(145)*	34 *(179)*	25 *(204)*	*22 (226)*
28	52	31 *(83)*	33 *(116)*	30 *(146)*	19 *(165)*	18 *(183)*
29	56	47 *(103)*	33 *(136)*	28 *(164)*	21 *(185)*	21 *(206)*
30	60	45 *(105)*	34 *(139)*	24 *(163)*	24 *(187)*	2 *(189)*

P = animals paired for mating
( ) = *cumulative bodyweight change relative to Day 1*

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 4 (continued) Bodyweights and Bodyweight Change for Males - Individual Values

DOSE LEVEL: 175 mg/kg/day

Animal Number	Bodyweight (g) at Day						
	1	8	15 P	22	29	36	43
41	307	371	399	443	488	504	509
42	286	342	392	435	474	507	519
43	290	343	385	402	421	446	446
44	317	358	392	416	441	456	450
45	291	330	344	381	414	443	441
46	301	352	387	424	442	458	462
47	281	347	394	434	465	500	519
48	303	359	418	455	490	518	547
49	321	377	420	453	487	507	528
50	299	354	391	437	466	488	507

Animal Number	Bodyweight Change (g) during Week					
	1	2	3 P	4	5	6
41	*64*	28 *(92)*	44 *(136)*	45 *(181)*	16 *(197)*	5 *(202)*
42	*56*	*50 (106)*	43 *(149)*	39 *(188)*	33 *(221)*	12 *(233)*
43	53	42 *(95)*	17 *(112)*	19 *(131)*	25 *(156)*	0 *(156)*
44	41	34 *(75)*	24 *(99)*	25 *(124)*	15 *(139)*	-6 *(133)*
45	*39*	14 *(53)*	37 *(90)*	33 *(123)*	29 *(152)*	-2 *(150)*
46	51	35 *(86)*	37 *(123)*	18 *(141)*	16 *(157)*	4 *(161)*
47	*66*	47 *(113)*	40 *(153)*	31 *(184)*	35 *(219)*	*19 (238)*
48	56	59 *(115)*	37 *(152)*	35 *(187)*	28 *(215)*	29 *(244)*
49	56	43 *(99)*	33 *(132)*	34 *(166)*	20 *(186)*	21 *(207)*
50	55	37 *(92)*	46 *(138)*	29 *(167)*	22 *(189)*	19 *(208)*

P = animals paired for mating
( ) = *cumulative bodyweight change relative to Day 1*

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 4 (continued) Bodyweights and Bodyweight Change for Males - Individual Values

DOSE LEVEL: 600 mg/kg/day

Animal Number	Bodyweight (g) at Day								
	1	8	15 P	22	29	36	43	50	57
61	334	380	408	439	470	493	482	-	-
62	285	333	355	379	411	438	412	-	-
63	294	303	309	328	345	356	344	-	-
64	289	322	357	386	407	421	410	-	-
65	290	321	349	376	394	407	399	-	-
66	306	356	392	421	449	466	471	-	-
67	294	337	367	396	424	435	440	-	-
68	296	330	344	375	393	420	422	-	-
69	286	336	358	389	405	418	420	-	-
70	314	346	353	382	390	395	402	-	-
91	305	334	374	412	419	442	442	450	461
92	299	340	381	418	446	467	477	481	493
93	304	340	383	422	447	464	460	490	526
94	274	329	365	399	416	428	417	410	429
95	308	335	366	394	■	408	412	414	422

Animal Number	Bodyweight Change (g) during Week							
	1	2	3	4	5	6	7	8
61	46	28 *(74)*	31 *(105)*	31 *(136)*	23 *(159)*	-11 *(148)*	-	-
62	48	*22 (70)*	24 *(94)*	32 *(126)*	27 *(153)*	-26 *(127)*	-	-
63	9	6 *(15)*	19 *(34)*	17 *(51)*	11 *(62)*	-12 *(50)*	-	-
64	33	35 *(68)*	29 *(97)*	21 *(118)*	14 *(132)*	-11 *(121)*	-	-
65	*31*	28 *(59)*	27 *(86)*	18 *(104)*	13 *(117)*	-8 *(109)*	-	-
66	50	36 *(86)*	29 *(115)*	28 *(143)*	17 *(160)*	5 *(165)*	-	-
67	*43*	30 *(73)*	29 *(102)*	28 *(130)*	11 *(141)*	*5 (146)*	-	-
68	34	14 *(48)*	31 *(79)*	18 *(97)*	27 *(124)*	2 *(126)*	-	-
69	50	22 *(72)*	31 *(103)*	16 *(119)*	13 *(132)*	2 *(134)*	-	-
70	32	7 *(39)*	29 *(68)*	8 *(76)*	5 *(81)*	7 *(88)*	-	-
91	29	40 *(69)*	38 *(107)*	7 *(114)*	23 *(137)*	0 *(137)*	8 *(145)*	11 *(156)*
92	41	41 *(82)*	37 *(119)*	28 *(147)*	21 *(168)*	10 *(178)*	4 *(182)*	12 *(194)*
93	36	43 *(79)*	39 *(118)*	25 *(143)*	17 *(160)*	-4 *(156)*	30 *(186)*	36 *(222)*
94	55	36 *(91)*	34 *(125)*	17 *(142)*	12 *(154)*	-11 *(143)*	-7 *(136)*	19 *(155)*
95	27	31 *(58)*	28 *(86)*	■	■ *(100)*	4 *(104)*	2 *(106)*	8 *(114)*

P = animals paired for mating
■ = data unavailable
( ) = *cumulative bodyweight change relative to Day 1*

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 5 Bodyweight and Bodyweight Change for Females - Individual Values

Non-Recovery Females

DOSE LEVEL: 0 (Control)

Animal Number	Bodyweight (g) at Day								
	Maturation			Gestation				Lactation	
	1	8	15	0	7	14	20	1	4
11	161	189	197	204	239	278	374	261	269
12	195	213	229	246	288	320	394	311	330
13	178	205	226	230	251	299	387	278	296
14	197	214	244	238	278	326	374	327	324
15KIE	176	199	212	219	265	321	395	-	-
16	183	219	235	239	286	332	414	321	340
17	172	191	287	206	262	307	404	308	329
18	184	210	233	240	276	323	408	318	334
19	199	212	244	242	281	318	410	302	322
20	204	230	243	222	289	337	422	327	339

Animal Number	Bodyweight Change (g) during					
	Maturation		Gestation			Lactation
	Week 1	Week 2	Days 0 - 7	Days 7 - 14	Days 14 - 20	Days 1 - 4
11	28	8 *(36)*	35	39 *(74)*	96 *(170)*	8
12	18	16 *(34)*	42	32 *(74)*	74 *(148)*	19
13	27	21 *(48)*	21	48 *(69)*	88 *(157)*	18
14	17	30 *(47)*	40	48 *(88)*	48 *(136)*	-3
15	23	13 *(36)*	46	56 *(102)*	74 *(176)*	-
16	36	16 *(52)*	47	46 *(93)*	82 *(175)*	19
17	19	96 *(115)*	56	45 *(101)*	97 *(198)*	21
18	26	23 *(49)*	36	47 *(83)*	85 *(168)*	16
19	13	32 *(45)*	39	37 *(76)*	92 *(168)*	20
20	26	13 *(39)*	67	48 *(115)*	85 *(200)*	12

KIE = killed *in extremis* – Day 22 gestation
- = not applicable
( ) = *cumulative bodyweight change relative to Day 1 of phase*

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 5 (continued) Bodyweight and Bodyweight Change for Females - Individual Values

Non-Recovery Females

DOSE LEVEL: 50 mg/kg/day

Animal Number	Bodyweight (g) at Day								
	Maturation			Gestation				Lactation	
	1	8	15	0	7	14	20	1	4
31	194	219	232	236	283	331	412	317	324
32	192	204	222	230	269	311	400	292	308
33	190	201	209	233	270	305	385	288	303
34	175	216	226	230	286	333	434	328	343
35	185	200	222	225	262	303	368	290	318
36	190	196	217	219	258	289	359	289	301
37	175	194	206	210	246	284	360	258	268
38	194	225	241	249	292	336	417	322	346
39	190	208	230	233	285	327	425	333	342
40 NP	174	191	209	-	-	-	-	-	-

Animal Number	Bodyweight Change (g) during					
	Maturation		Gestation			Lactation
	Week 1	Week 2	Days 0 - 7	Days 7 - 14	Days 14 - 20	Days 1 - 4
31	25	13 *(38)*	47	48 *(95)*	81 *(176)*	7
32	12	18 *(30)*	39	42 *(81)*	89 *(170)*	16
33	11	8 *(19)*	37	35 *(72)*	80 *(152)*	15
34	41	10 *(51)*	56	47 *(103)*	101 *(204)*	15
35	15	22 *(37)*	37	41 *(78)*	65 *(143)*	28
36	6	21 *(27)*	39	31 *(70)*	70 *(140)*	12
37	19	12 *(31)*	36	38 *(74)*	76 *(150)*	10
38	31	16 *(47)*	43	44 *(87)*	81 *(168)*	24
39	18	22 *(40)*	52	42 *(94)*	98 *(192)*	9
40 NP	17	18 *(35)*	-	-	-	-

NP = not pregnant
- = not applicable
( ) = *cumulative bodyweight change relative to Day 1 of phase*

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 5 (continued) Bodyweight and Bodyweight Change for Females - Individual Values

Non-Recovery Females

DOSE LEVEL: 175 mg/kg/day

Animal Number	Bodyweight (g) at Day								
	Maturation			Gestation				Lactation	
	1	8	15	0	7	14	20	1	4
51	193	212	225	226	266	309	389	316	330
52	200	213	222	239	299	335	415	334	355
53	190	200	216	215	267	319	394	303	325
54	176	201	212	217	264	322	408	319	325
55	197	216	249	246	294	341	418	327	356
56	178	205	218	220	264	311	390	310	330
57	174	202	220	218	264	310	391	302	311
58	194	211	226	227	261	305	395	308	317
59	171	188	227	212	255	298	383	284	300
60	186	207	209	220	263	301	382	291	304

Animal Number	Bodyweight Change (g) during					
	Maturation		Gestation			Lactation
	Week 1	Week 2	Days 0 - 7	Days 7 - 14	Days 14 - 20	Days 1 - 4
51	19	13 *(32)*	40	43 *(83)*	80 *(163)*	14
52	13	9 *(22)*	60	36 *(96)*	80 *(176)*	21
53	10	16 *(26)*	52	52 *(104)*	75 *(179)*	22
54	25	11 *(36)*	47	58 *(105)*	86 *(191)*	6
55	19	33 *(52)*	48	47 *(95)*	77 *(172)*	29
56	27	13 *(40)*	44	47 *(91)*	79 *(170)*	20
57	28	18 *(46)*	46	46 *(92)*	81 *(173)*	9
58	17	15 *(32)*	34	44 *(78)*	90 *(168)*	9
59	17	39 *(56)*	43	43 *(86)*	85 *(171)*	16
60	21	2 *(23)*	43	38 *(81)*	81 *(162)*	13

( ) = *cumulative bodyweight change relative to Day 1 of phase*

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 5 (continued) Bodyweight and Bodyweight Change for Females - Individual Values

Non-Recovery Females

DOSE LEVEL: 600 mg/kg/day

Animal Number	Bodyweight (g) at Day								
	Maturation			Gestation				Lactation	
	1	8	15	0	7	14	20	1	4
71	183	204	219	220	254	298	371	269	287
72	186	200	210	210	250	290	354	271	285
73	191	213	230	232	265	294	348	284	297
74	201	227	243	239	281	314	395	295	309
75	192	208	224	220	266	314	385	285	299
76	194	209	216	229	271	317	404	285	303
77	190	213	231	230	272	317	388	302	317
78	181	198	212	211	253	297	372	290	300
79	182	210	230	237	280	316	373	267	291
80	180	201	207	222	263	299	383	291	291

Animal Number	Bodyweight Change (g) during					
	Maturation		Gestation			Lactation
	Week 1	Week 2	Days 0 - 7	Days 7 - 14	Days 14 - 20	Days 1 - 4
71	21	15 *(36)*	34	44 *(78)*	73 *(151)*	18
72	14	10 *(24)*	40	40 *(80)*	64 *(144)*	14
73	22	17 *(39)*	33	29 *(62)*	54 *(116)*	13
74	26	16 *(42)*	42	33 *(75)*	81 *(156)*	14
75	16	16 *(32)*	46	48 *(94)*	71 *(165)*	14
76	15	7 *(22)*	42	46 *(88)*	87 *(175)*	18
77	23	18 *(41)*	42	45 *(87)*	71 *(158)*	15
78	17	14 *(31)*	42	44 *(86)*	75 *(161)*	10
79	28	20 *(48)*	43	36 *(79)*	57 *(136)*	24
80	21	6 *(27)*	41	36 *(77)*	84 *(161)*	0

( ) = *cumulative bodyweight change relative to Day 1 of phase*

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 5 (continued) Bodyweight and Bodyweight Change for Females - Individual Values

Recovery Females

DOSE LEVEL: 0 (control)

Animal Number	Bodyweight (g) at Day								
	1	8	15	22	29	36	43	50	57
86	167	197	219	236	238	255	261	263	263
87	197	223	238	244	266	274	283	284	300
88	193	208	225	241	246	249	261	264	264
89	204	224	248	256	278	289	292	289	298
90	197	216	220	258	267	281	273	298	303

Animal Number	Bodyweight Change (g) during Week							
	1	2	3	4	5	6	7	8
86	30	22 *(52)*	17 *(69)*	2 *(71)*	17 *(88)*	6 *(94)*	2 *(96)*	0 *(96)*
87	26	15 *(41)*	6 *(47)*	22 *(69)*	8 *(77)*	9 *(86)*	1 *(87)*	16 *(103)*
88	15	17 *(32)*	16 *(48)*	5 *(53)*	3 *(56)*	12 *(68)*	3 *(71)*	0 *(71)*
89	20	24 *(44)*	8 *(52)*	22 *(74)*	11 *(85)*	3 *(88)*	-3 *(85)*	9 *(94)*
90	19	4 *(23)*	38 *(61)*	9 *(70)*	14 *(84)*	-8 *(76)*	25 *(101)*	5 *(106)*

( ) *cumulative bodyweight change relative to Day 1*

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 5 (continued) Bodyweight and Bodyweight Change for Females - Individual Values

Recovery Females

DOSE LEVEL: 600 mg/kg/day

Animal Number	Bodyweight (g) at Day								
	1	8	15	22	29	36	43	50	57
96	180	211	235	246	275	281	283	275	288
97	173	197	209	215	232	245	243	237	259
98	197	227	240	268	278	290	283	279	286
99	192	206	221	240	242	259	263	265	270
100	187	203	211	221	226	239	248	257	257

Animal Number	Bodyweight Change (g) during Week							
	1	2	3	4	5	6	7	8
96	31	24 (55)	11 (66)	29 (95)	6 (101)	2 (103)	-8 (95)	13 (108)
97	24	12 (36)	6 (42)	17 (59)	13 (72)	-2 (70)	-6 (64)	22 (86)
98	30	13 (43)	28 (71)	10 (81)	12 (93)	-7 (86)	-4 (82)	7 (89)
99	14	15 (29)	19 (48)	2 (50)	17 (67)	4 (71)	2 (73)	5 (78)
100	16	8 (24)	10 (34)	5 (39)	13 (52)	9 (61)	9 (70)	0 (70)

( ) = *cumulative bodyweight change relative to Day 1*

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 6 Food Consumption for Females during Gestation and Lactation - Individual Values

DOSE LEVEL: 0 (control)

Animal Number	Mean Food Consumption (g/rat/day) during			
	Gestation			Lactation
	Days 1 - 7	Days 7 - 14	Days 14 - 20	Days 1-4
11	21	22	24	34
12	24	24	26	39
13	19	21	22	33
14	23	24	24	27
15 KIE	19	22	20	-
16	24	24	25	40
17	22	23	23	38
18	20	23	24	39
19	19	21	25	31
20	20	23	24	43

KIE = killed *in extremis* – Day 22 gestation
- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 6 (continued) Food Consumption for Females during Gestation and Lactation - Individual values

DOSE LEVEL: 50 mg/kg/day

Animal Number	Mean Food Consumption (g/rat/day) during			
	Gestation			Lactation
	Days 1 - 7	Days 7 - 14	Days 14 - 20	Days 1-4
31	24	26	26	29
32	22	24	24	34
33	21	22	23	30
34	24	29	28	45
35	20	22	23	40
36	19	19	20	36
37	22	23	22	29
38	24	25	24	39
39	22	23	24	42
40 NP	-	-	-	-

NP = not pregnant
- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 6 (continued) Food Consumption for Females during Gestation and Lactation - Individual values

DOSE LEVEL: 175 mg/kg/day

Animal Number	Mean Food Consumption (g/rat/day) during			
	Gestation			Lactation
	Days 1 - 7	Days 7 - 14	Days 14 - 20	Days 1-4
51	22	23	22	45
52	25	27	27	39
53	20	23	23	40
54	24	25	26	41
55	24	24	24	40
56	20	21	23	43
57	20	21	21	39
58	18	21	23	43
59	23	24	23	31
60	19	22	21	36

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 6 (continued) Food Consumption for Females during Gestation and Lactation - Individual values

DOSE LEVEL: 600 mg/kg/day

Animal Number	Mean Food Consumption (g/rat/day) during Gestation			Lactation
	Days 1 - 7	Days 7 - 14	Days 14 - 20	Days 1-4
71	20	22	23	32
72	13	22	21	32
73	20	21	21	29
74	24	24	24	31
75	22	24	25	32
76	23	25	25	35
77	22	24	25	34
78	20	21	22	33
79	23	23	19	36
80	22	24	26	31

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 7 Water Consumption for Females during Gestation and Lactation - Individual Values

DOSE LEVEL: 0 (Control)

Animal Number	Mean Water Consumption (g/rat/day) during Gestation (Day)																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
11	22	35	41	49	46	43	49	44	48	44	43	44	40	49	56	44	51	61	122	42	60
12	37	33	38	51	44	37	44	39	43	42	45	36	53	42	43	48	47	46	47	51	43
13	22	32	33	27	28	25	26	33	28	35	29	32	34	34	30	41	42	42	44	39	36
14	30	33	35	34	33	38	36	40	35	46	43	35	38	40	35	42	44	47	45	47	34
15 KIE	23	31	37	36	29	36	40	39	39	41	42	31	36	38	37	43	43	45	23	49	28
16	24	32	40	31	38	38	36	36	44	43	37	48	47	44	48	54	47	49	56	40	43
17	22	25	21	24	33	28	25	24	34	36	25	38	32	29	29	44	64	41	45	38	41
18	21	26	28	31	32	27	29	28	31	29	30	31	38	36	36	36	42	49	39	43	50
19	21	26	26	31	26	33	26	24	30	37	37	33	29	30	36	42	43	38	41	39	28
20	31	37	44	46	35	38	39	38	43	48	47	39	44	40	42	49	51	55	52	54	43

Animal Number	Mean Water Consumption (g/rat/day) during Lactation (Day)			
	1	2	3	4
11	54	54	64	58
12	56	54	76	66
13	33	57	55	50
14	47	41	40	50
15 KIE	-	-	-	-
16	51	62	68	64
17	54	50	58	54
18	47	55	58	56
19	39	48	49	62
20	53	75	68	81

KIE = killed *in extremis*
- = data not available

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 7 (continued) Water Consumption for Females during Gestation and Lactation - Individual Values

DOSE LEVEL: 50 mg/kg/day

Animal Number	Mean Water Consumption (g/rat/day) during Gestation (Day)																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
31	27	28	27	36	34	31	31	36	38	42	35	37	38	34	34	50	46	44	44	43	47
32	22	33	33	37	35	35	35	39	31	43	42	42	40	40	43	46	47	56	47	49	36
33	25	27	25	37	28	30	39	35	35	28	32	33	41	37	42	35	48	36	45	40	37
34	36	35	40	39	35	40	46	144	41	54	43	38	42	58	52	56	54	61	49	56	41
35	28	36	33	37	34	36	44	36	37	40	48	36	42	49	42	48	48	52	54	59	57
36	32	37	37	39	44	38	41	33	40	43	43	31	38	36	31	44	48	44	50	44	36
37	23	26	34	34	29	30	29	30	35	37	34	41	35	32	30	43	43	42	43	42	37
38	32	43	45	42	45	43	39	42	47	40	42	46	44	43	43	50	42	52	43	52	43
39	35	41	47	47	43	50	46	42	44	55	57	47	50	56	52	50	63	68	54	48	52
40 NP																					

Animal Number	Mean Water Consumption (g/rat/day) during Lactation (Day)			
	1	2	3	4
31	41	50	53	62
32	53	53	57	63
33	46	44	65	72
34	64	68	71	66
35	50	68	71	78
36	45	67	65	71
37	37	51	42	59
38	54	63	69	62
39	54	60	63	66
40 NP				

NP = not pregnant

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 7 (continued) Water Consumption for Females during Gestation and Lactation - Individual values

DOSE LEVEL: 175 mg/kg/day

Animal Number	Mean Water Consumption (g/rat/day) during Gestation (Day)																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
51	40	47	45	52	45	45	37	33	44	43	37	43	39	42	38	52	56	48	54	47	46
52	39	40	44	61	51	45	54	48	51	47	54	58	56	55	50	55	66	51	64	58	62
53	32	33	31	37	39	38	38	38	36	42	49	42	37	42	40	47	51	46	47	53	40
54	33	40	43	40	38	44	36	40	52	48	42	47	43	56	53	55	62	55	62	47	46
55	26	34	36	42	37	35	38	58	45	42	67	38	44	42	45	48	53	45	39	49	44
56	31	29	28	32	32	33	35	31	38	41	36	44	41	42	41	47	49	59	52	43	46
57	19	35	23	35	35	31	29	28	31	40	32	34	34	28	37	35	43	39	49	38	47
58	25	32	37	37	37	40	37	44	35	42	44	38	47	44	45	49	53	49	52	59	50
59	33	33	29	36	41	40	42	44	47	53	40	44	44	44	49	48	53	54	58	51	57
60	25	31	42	35	28	36	32	31	153	50	32	50	29	32	37	52	41	48	58	41	48

Animal Number	Mean Water Consumption (g/rat/day) during Lactation (Day)			
	1	2	3	4
51	48	78	76	82
52	58	63	69	83
53	50	57	68	56
54	76	69	66	90
55	54	65	64	74
56	53	68	79	74
57	57	60	64	74
58	63	67	68	83
59	51	52	51	55
60	54	54	68	55

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 7 (continued) Water Consumption for Females during Gestation and Lactation - Individual values

DOSE LEVEL: 600 mg/kg/day

Animal Number	Mean Water Consumption (g/rat/day) during Gestation (Day)																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
71	35	33	39	41	38	37	37	42	47	45	40	46	46	43	50	51	59	52	60	50	54
72	40	38	60	45	53	38	54	47	63	60	45	56	56	54	54	59	61	56	55	42	52
73	40	42	45	50	54	51	50	51	70	40	45	47	88	34	51	55	49	51	50	49	54
74	43	56	56	49	51	54	58	55	69	74	52	85	81	69	79	66	77	84	82	62	42
75	35	43	45	49	46	46	77	51	52	56	64	53	54	71	54	67	62	59	60	60	38
76	35	33	32	37	37	40	41	45	37	44	42	54	52	61	54	53	-	53	57	57	55
77	34	37	38	44	39	43	40	41	53	53	44	48	51	57	56	58	70	54	55	50	49
78	27	32	33	43	38	40	37	38	43	42	40	39	42	40	44	48	49	43	46	45	48
79	47	50	52	51	52	53	56	60	58	55	55	74	67	71	67	93	78	48	66	77	-
80	19	38	34	36	36	35	47	53	40	42	40	47	53	47	48	49	51	45	64	54	54

Animal Number	Mean Water Consumption (g/rat/day) during Lactation (Day)			
	1	2	3	4
71	48	66	69	66
72	53	57	72	51
73	43	45	64	71
74	42	52	69	73
75	57	49	66	65
76	57	45	67	49
77	55	64	73	59
78	46	47	64	67
79	69	90	78	89
80	51	73	55	75

- = data unavailable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 Haematology - Individual Values

Day 14 - Non-Recovery Males

DOSE LEVEL: 0 (Control)

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
1	14.1	7.03	41.1	20.0	58.0	34.3	15.5
2	15.2	7.55	42.8	20.1	57.0	35.5	13.7
3	14.5	7.50	41.0	19.3	55.0	35.3	8.9
4	16.1	7.59	45.3	21.2	60.0	35.4	12.5
5	13.7	6.97	39.6	19.7	57.0	34.7	12.8

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
1	1.40	13.95	0.16	0.00	0.00	17.5	994	14.7
2	1.37	12.33	0.00	0.00	0.00	17.7	1023	16.8
3	0.89	8.01	0.00	0.00	0.00	15.0	933	14.3
4	2.00	10.50	0.00	0.00	0.00	20.9	1093	19.8
5	1.28	11.26	0.00	0.26	0.00	16.7	996	14.2

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 14 - Non Recovery Females

DOSE LEVEL: 0 (Control)

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
11	15.2	7.51	42.7	20.2	57.0	35.5	8.3
12	14.0	7.04	39.0	19.8	55.0	35.7	7.9
13	-	-	-	-	-	-	-
14	14.6	6.74	40.3	21.6	60.0	36.1	10.4
15	14.2	7.39	40.2	19.3	54.0	35.4	5.9

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
11	0.58	7.64	0.00	0.08	0.00	22.4	946	16.2
12	0.71	7.19	0.00	0.00	0.00	18.6	940	16.0
13	-	-	-	-	-	16.3	-	16.6
14	0.83	9.57	0.00	0.00	0.00	15.8	1018	15.5
15	0.59	5.31	0.00	0.00	0.00	15.7	987	15.9

- = data unavailable; sample clotted

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 14 - Non-Recovery Males

DOSE LEVEL: 50 mg/kg/day

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
21	15.4	7.71	42.5	20.0	55.0	36.1	8.7
22	14.9	7.62	43.7	19.6	57.0	34.1	14.2
23	14.9	7.65	43.7	19.5	57.0	34.2	12.5
24	14.7	7.18	42.6	20.4	59.0	34.5	11.3
25	15.2	7.82	43.0	19.5	55.0	35.4	10.1

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
21	1.39	7.13	0.00	0.17	0.00	18.4	885	17.2
22	1.28	12.92	0.00	0.00	0.00	16.4	865	14.7
23	2.50	10.00	0.00	0.00	0.00	16.8	911	13.9
24	1.02	10.28	0.00	0.00	0.00	14.4	923	13.8
25	1.11	8.99	0.00	0.00	0.00	16.5	986	16.8

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 14 - Non-Recovery Females

DOSE LEVEL: 50 mg/kg/day

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
31	14.0	6.94	38.6	20.2	56.0	36.4	5.7
32	14.9	7.51	42.4	19.8	57.0	35.0	8.9
33	-	-	-	-	-	-	-
34	14.8	7.50	41.1	19.7	55.0	36.0	6.7
35	15.0	7.82	42.7	19.2	55.0	35.2	11.5

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
31	0.29	5.30	0.00	0.11	0.00	14.6	1160	14.1
32	0.71	8.10	0.00	0.09	0.00	14.8	892	14.0
33	-	-	-	-	-	22.4	-	17.0
34	0.67	5.90	0.00	0.13	0.00	21.3	595	15.9
35	0.58	10.70	0.00	0.23	0.00	15.0	978	15.5

- = data unavailable; sample clotted

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 14 - Non-Recovery Males

DOSE LEVEL: 175 mg/kg/day

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
41	15.4	7.37	44.9	20.9	61.0	34.4	13.7
42	14.8	6.45	40.7	22.9	63.0	36.3	10.8
43	14.8	7.72	43.2	19.1	56.0	34.1	11.3
44	15.3	7.87	44.6	19.4	57.0	34.3	11.6
45	15.4	7.88	44.2	19.5	56.0	34.8	14.0

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
41	3.29	10.28	0.00	0.14	0.00	17.1	942	13.7
42	0.76	9.94	0.00	0.11	0.00	14.1	1166	13.6
43	1.47	9.83	0.00	0.00	0.00	18.3	1090	15.7
44	1.04	10.44	0.00	0.12	0.00	18.6	975	14.8
45	3.22	10.64	0.00	0.14	0.00	16.2	934	17.3

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 14 -Non-Recovery Females

DOSE LEVEL: 175 mg/kg/day

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
51	14.8	7.60	41.5	19.5	55.0	35.6	11.7
52	14.4	6.93	39.9	20.7	58.0	36.0	6.7
53	14.2	7.22	39.9	19.7	55.0	35.7	12.2
54	15.3	7.67	42.6	19.9	56.0	35.9	7.3
55	13.9	7.05	39.6	19.7	56.0	35.1	13.0

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
51	0.94	10.76	0.00	0.00	0.00	15.3	878	16.0
52	0.80	5.83	0.00	0.07	0.00	13.4	1061	12.6
53	5.86	6.22	0.00	0.12	0.00	18.4	943	14.8
54	1.02	6.21	0.00	0.07	0.00	-	911	16.5
55	1.56	11.31	0.00	0.13	0.00	18.1	828	13.5

- = data unavailable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 14 -Non-Recovery Males

DOSE LEVEL: 600 mg/kg/day

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
61	15.1	7.31	44.2	20.7	60.0	34.2	10.5
62	14.6	7.30	42.7	20.0	59.0	34.2	19.0
63	15.9	8.55	46.2	18.6	54.0	34.5	12.6
64	14.2	7.63	41.2	18.6	54.0	34.4	15.3
65	14.8	7.32	43.2	20.3	59.0	34.4	14.4

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
61	1.58	8.82	0.00	0.11	0.00	12.4	1025	9.3
62	2.09	16.72	0.00	0.19	0.00	16.1	929	16.6
63	2.65	9.95	0.00	0.00	0.00	18.1	843	15.2
64	1.84	13.46	0.00	0.00	0.00	14.0	813	12.9
65	4.18	10.08	0.00	0.14	0.00	14.5	961	15.3

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 14 - Non-Recovery Females

DOSE LEVEL: 600 mg/kg/day

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
71	14.2	7.17	39.7	19.9	55.0	35.9	9.1
72	15.2	7.48	42.6	20.3	57.0	35.5	7.5
73	14.7	7.25	41.2	20.2	57.0	35.6	10.7
74	15.1	7.71	42.4	19.6	55.0	35.5	7.4
75	14.2	7.30	40.6	19.4	56.0	34.9	7.0

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
71	1.00	8.10	0.00	0.00	0.00	21.0	999	16.5
72	0.53	6.98	0.00	0.00	0.00	14.4	871	15.8
73	0.86	9.84	0.00	0.00	0.00	15.9	1207	16.2
74	0.59	6.66	0.00	0.15	0.00	-	973	15.6
75	0.91	6.02	0.00	0.07	0.00	16.3	907	13.8

- = data unavailable; sample would not clot

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 42 -Non-Recovery Males

DOSE LEVEL: 0 (Control)

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
1	15.0	7.91	44.7	19.0	56.0	33.6	13.8
2	16.2	8.72	47.0	18.6	54.0	34.5	13.6
3	15.7	8.64	46.2	18.1	53.0	34.0	11.4
4	16.8	8.58	49.3	19.6	57.0	34.1	15.0
5	15.4	8.45	45.7	18.2	54.0	33.7	13.0

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
1	1.93	11.87	0.00	0.00	0.00	16.5	717	13.0
2	2.04	11.42	0.00	0.14	0.00	16.5	899	14.1
3	1.37	9.92	0.00	0.11	0.00	14.5	700	10.4
4	2.70	12.30	0.00	0.00	0.00	23.7	823	19.0
5	2.08	10.53	0.00	0.39	0.00	14.5	731	10.7

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 5 *post partum* - Non-Recovery Females

DOSE LEVEL: 0 (Control)

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
11	13.2	6.78	39.8	19.5	59.0	33.3	7.9
12	12.1	6.45	35.7	18.7	55.0	33.8	5.6
13	11.7	5.93	34.1	19.6	57.0	34.2	6.6
14	13.8	6.84	40.0	20.1	58.0	34.5	11.8
16	12.6	6.61	36.7	19.0	56.0	34.2	4.4

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
11	0.71	7.19	0.00	0.00	0.00	18.6	503	14.9
12	0.62	4.87	0.00	0.11	0.00	16.9	736	11.9
13	0.59	6.01	0.00	0.00	0.00	15.3	769	10.6
14	3.19	8.61	0.00	0.00	0.00	15.5	817	12.7
16	0.40	3.87	0.00	0.13	0.00	15.8	701	13.8

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 42 - Non-Recovery Males

DOSE LEVEL: 50 mg/kg/day

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
21	16.1	8.70	47.6	18.5	55.0	33.8	10.3
22	16.2	8.93	49.3	18.1	55.0	32.9	13.1
23	15.6	8.30	46.5	18.8	56.0	33.5	11.1
24	16.1	8.25	47.2	19.5	57.0	34.1	10.4
25	15.3	8.52	44.6	18.0	52.0	34.3	12.0

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
21	2.06	7.83	0.00	0.41	0.00	18.7	717	14.9
22	1.05	11.92	0.00	0.13	0.00	16.1	655	14.1
23	1.55	9.32	0.00	0.22	0.00	20.3	686	14.6
24	1.25	8.84	0.00	0.31	0.00	16.0	726	11.3
25	2.88	9.12	0.00	0.00	0.00	14.8	771	12.7

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 5 *post partum* - Non-Recovery Females

DOSE LEVEL: 50 mg/kg/day

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
31	12.2	6.24	36.5	19.6	59.0	33.5	6.5
32	12.2	6.38	37.2	19.2	58.0	32.8	4.8
33	11.0	5.66	32.8	19.5	58.0	33.7	6.0
34	11.6	6.48	34.9	17.9	54.0	33.2	6.3
35	11.8	6.36	37.0	18.6	58.0	32.0	6.7

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
31	1.63	4.75	0.00	0.13	0.00	13.8	979	10.9
32	0.53	4.22	0.00	0.05	0.00	14.7	804	11.9
33	0.54	5.46	0.00	0.00	0.00	15.9	693	10.1
34	1.83	4.47	0.00	0.00	0.00	15.3	772	13.6
35	1.21	5.49	0.00	0.00	0.00	16.7	878	14.8

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 42 - Non-Recovery Males

DOSE LEVEL: 175 mg/kg/day

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
41	16.1	8.39	47.8	19.2	57.0	33.8	9.9
42	16.6	7.76	46.4	21.4	60.0	35.9	9.6
43	15.6	8.66	46.2	18.0	53.0	33.6	13.7
44	16.3	8.86	46.2	18.4	52.0	35.2	11.5
45	15.7	8.46	46.2	18.6	55.0	34.0	15.0

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
41	1.78	8.02	0.00	0.10	0.00	21.9	784	14.1
42	0.48	9.12	0.00	0.00	0.00	12.6	872	10.6
43	4.11	9.32	0.00	0.27	0.00	11.3	779	9.4
44	0.92	10.47	0.00	0.12	0.00	14.5	780	11.4
45	3.00	11.85	0.00	0.15	0.00	13.9	785	12.2

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 5 *post partum* - Non-Recovery Females

DOSE LEVEL: 175 mg/kg/day

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
51	12.6	6.58	38.5	19.2	58.0	32.9	7.7
52	12.5	6.01	37.2	20.7	62.0	33.5	5.2
53	11.7	6.08	35.5	19.2	58.0	32.8	9.9
54	12.9	6.23	38.3	20.8	61.0	33.8	6.0
55	12.0	6.00	34.8	20.0	58.0	34.4	16.1

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
51	0.69	6.93	0.00	0.08	0.00	19.2	564	14.3
52	0.68	4.47	0.00	0.05	0.00	14.0	883	8.2
53	2.97	6.93	0.00	0.00	0.00	15.5	921	13.2
54	1.14	4.86	0.00	0.00	0.00	18.2	760	9.6
55	4.99	10.95	0.00	0.16	0.00	-	604	-

- = data unavailable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 42 - Non-Recovery Males

DOSE LEVEL: 600 mg/kg/day

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
61	16.1	8.36	47.9	19.3	57.0	33.7	12.4
62	16.4	8.83	48.7	18.5	55.0	33.6	17.4
63	15.9	9.21	47.9	17.3	52.0	33.3	15.4
64	15.7	9.01	47.6	17.5	53.0	33.1	16.3
65	16.0	8.58	47.5	18.7	55.0	33.7	11.1

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
61	0.99	11.28	0.00	0.12	0.00	20.1	771	16.9
62	3.13	13.92	0.00	0.35	0.00	15.6	764	12.4
63	3.85	11.40	0.00	0.15	0.00	19.0	778	12.3
64	0.49	15.49	0.00	0.33	0.00	16.6	710	14.0
65	0.56	10.21	0.00	0.33	0.00	14.3	673	11.9

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 5 *post partum* - Non-Recovery Females

DOSE LEVEL: 600 mg/kg/day

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
71	12.9	6.89	39.2	18.7	57.0	32.8	9.2
72	13.3	6.75	40.2	19.7	60.0	33.1	7.1
73	12.2	6.56	35.9	18.6	55.0	33.9	4.2
74	12.3	6.66	37.0	18.5	56.0	33.2	6.8
75	12.5	6.61	39.2	18.9	59.0	32.0	7.7

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
71	1.66	7.54	0.00	0.00	0.00	15.6	569	12.1
72	0.78	6.32	0.00	0.00	0.00	15.8	613	11.9
73	0.00	4.20	0.00	0.00	0.00	19.3	-	11.5
74	1.84	4.96	0.00	0.00	0.00	15.4	580	11.6
75	2.39	5.31	0.00	0.00	0.00	13.8	884	11.7

- = data unavailable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 56 - Recovery Males

DOSE LEVEL: 0 (Control) Recovery

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
81	16.5	9.05	50.8	18.3	56.0	32.6	11.5
82	15.1	8.77	45.8	17.2	52.0	33.0	14.4
83	15.4	8.36	45.7	18.4	55.0	33.7	9.8
84	15.8	8.63	47.1	18.3	55.0	33.4	12.1
85	15.5	8.31	45.5	18.7	55.0	34.1	10.7

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
81	0.92	10.47	0.00	0.12	0.00	17.3	656	17.2
82	2.88	11.52	0.00	0.00	0.00	17.2	789	15.1
83	1.37	8.43	0.00	0.00	0.00	15.8	689	15.1
84	1.09	10.65	0.00	0.36	0.00	16.1	865	16.0
85	1.93	8.67	0.00	0.11	0.00	16.1	732	14.6

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 56 - Recovery Females

DOSE LEVEL: 0 (Control) Recovery

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
86	14.9	7.47	42.9	19.9	57.0	34.7	10.6
87	14.3	8.05	41.8	17.8	52.0	34.2	6.3
88	14.6	8.21	43.1	17.8	53.0	33.8	9.8
89	14.0	7.55	41.1	18.5	54.0	34.0	7.1
90	15.7	7.97	45.6	19.7	57.0	34.4	9.2

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
86	1.17	9.43	0.00	0.00	0.00	13.6	920	13.4
87	1.26	4.98	0.00	0.06	0.00	15.8	741	13.5
88	1.08	8.53	0.00	0.20	0.00	14.7	644	14.0
89	1.56	5.54	0.00	0.00	0.00	14.7	884	12.0
90	0.74	8.37	0.00	0.09	0.00	16.8	775	13.5

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 56 - Recovery Males

DOSE LEVEL: 600 mg/kg/day Recovery

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
91	16.1	9.14	48.8	17.7	53.0	33.1	15.9
92	16.3	9.28	48.8	17.5	53.0	33.3	10.2
93	14.7	8.64	45.0	17.0	52.0	32.7	13.6
94	15.8	8.91	48.0	17.7	54.0	32.9	11.5
95	16.0	9.06	48.5	17.6	54.0	32.9	11.0

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
91	0.95	14.95	0.00	0.00	0.00	20.6	815	19.0
92	1.22	8.67	0.00	0.31	0.00	16.9	805	13.6
93	3.26	10.06	0.00	0.27	0.00	14.0	819	11.6
94	1.27	10.12	0.00	0.12	0.00	20.8	704	18.2
95	1.65	9.24	0.00	0.11	0.00	16.2	820	15.8

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 8 (continued) Haematology - Individual Values

Day 56 - Recovery Females

DOSE LEVEL: 600 mg/kg/day Recovery

Animal Number	Hb (g/dl)	RBC (10^{12}/l)	Hct (%)	MCH (pg)	MCV (fl)	MCHC (g/dl)	WBC (10^9/l)
96	14.3	8.18	43.2	17.5	53.0	33.2	8.3
97	14.4	7.89	42.2	18.2	54.0	34.0	7.6
98	14.1	8.38	42.3	16.8	50.0	33.4	7.5
99	14.7	8.80	44.5	16.7	51.0	33.1	9.7
100	13.4	8.25	41.3	16.2	50.0	32.5	9.8

Animal Number	Differential (10^9/l)					CT (secs)	PLT (10^9/l)	APTT (secs)
	Neut	Lymph	Mono	Eos	Bas			
96	0.75	7.47	0.00	0.08	0.00	16.5	892	14.4
97	0.61	6.92	0.00	0.08	0.00	20.6	919	18.0
98	0.83	6.53	0.00	0.15	0.00	13.3	778	13.7
99	0.39	9.31	0.00	0.00	0.00	15.0	914	14.6
100	1.27	8.53	0.00	0.00	0.00	15.5	1012	15.7

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 Blood Chemistry - Individual Values

Day 14 - Non-Recovery Males

DOSE LEVEL: 0 (Control)

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
1	39	197	6.31	3.88	1.60	149	4.34	106
2	32	167	6.38	3.68	1.36	148	4.79	103
3	35	172	5.96	3.63	1.56	147	4.96	105
4	35	138	6.50	3.84	1.44	146	4.48	103
5	33	166	6.35	3.66	1.36	147	4.66	104

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
1	2.63	2.2	61	43	372	0.77	86	0.13
2	2.69	2.3	71	31	354	0.76	74	0.17
3	2.76	2.5	73	48	456	0.78	65	0.07
4	2.88	2.5	70	48	514	0.79	64	0.13
5	2.78	1.7	71	51	326	0.75	76	0.10

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 14 - Non-Recovery Females

DOSE LEVEL: 0 (Control)

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
11	45	161	6.31	3.77	1.48	148	4.21	107
12	31	156	6.07	3.78	1.65	148	4.71	107
13	39	171	6.29	3.87	1.60	148	5.07	106
14	39	160	6.35	3.93	1.62	149	4.52	105
15	31	145	6.23	3.83	1.60	151	4.43	106

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
11	2.59	1.5	85	51	266	0.75	74	0.08
12	2.88	1.9	71	44	288	0.83	92	0.12
13	2.78	1.8	69	36	255	0.92	67	0.08
14	2.92	1.8	74	44	277	0.89	71	0.01
15	2.71	1.8	66	31	261	0.79	69	0.07

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 14 - Non-Recovery Males

DOSE LEVEL: 50 mg/kg/day

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
21	28	147	7.07	3.68	1.09	144	5.10	101
22	34	148	6.40	3.72	1.39	147	4.77	103
23	40	163	6.99	3.88	1.25	151	4.54	106
24	31	197	6.31	3.81	1.52	148	4.27	107
25	32	175	6.76	3.84	1.32	148	3.98	105

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
21	2.74	2.6	77	38	483	0.73	74	0.16
22	2.97	2.6	73	50	511	0.78	86	0.15
23	2.61	2.3	74	47	374	0.87	73	0.12
24	2.64	2.2	60	43	461	0.77	76	0.14
25	2.82	2.3	67	48	541	0.74	60	0.16

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 14 -Non-Recovery Females

DOSE LEVEL: 50 mg/kg/day

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
31	37	160	6.71	4.06	1.53	150	5.23	104
32	37	164	6.39	4.00	1.67	149	4.28	107
33	36	174	6.58	3.94	1.49	148	4.32	105
34	28	161	6.71	3.98	1.46	150	5.03	105
35	37	172	6.37	3.99	1.68	147	4.83	106

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
31	2.82	2.1	70	41	264	0.86	93	0.11
32	2.56	1.6	71	44	257	0.80	76	0.09
33	2.80	1.7	74	47	289	0.83	97	0.04
34	2.85	2.6	84	49	322	0.88	88	0.24
35	2.69	1.8	65	45	504	0.82	84	0.09

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 14 - Non-Recovery Males

DOSE LEVEL: 175 mg/kg/day

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
41	34	168	6.75	3.90	1.37	151	4.51	105
42	34	169	6.97	4.07	1.40	149	4.68	103
43	46	167	7.15	4.15	1.38	149	4.52	102
44	38	170	6.99	4.11	1.43	150	4.38	105
45	32	159	7.30	4.04	1.24	148	4.37	102

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
41	2.78	2.5	67	48	517	0.87	47	0.07
42	3.06	2.7	67	43	537	0.82	87	0.04
43	2.89	2.3	63	47	350	0.92	93	0.06
44	2.81	1.9	70	44	399	0.90	68	0.09
45	2.84	2.1	61	44	356	0.90	71	0.08

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 14 - Non-Recovery Females

DOSE LEVEL: 175 mg/kg/day

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
51	26	172	6.29	4.12	1.90	148	5.41	104
52	29	150	6.49	3.99	1.60	143	4.55	104
53	26	158	7.01	4.01	1.34	147	4.42	103
54	22	160	6.38	3.91	1.58	147	4.46	104
55	25	153	6.30	3.93	1.66	148	5.06	105

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
51	2.79	2.6	42	19	224	0.83	73	0.13
52	2.70	1.7	62	35	236	0.82	90	0.07
53	2.56	1.9	60	38	353	0.82	63	0.09
54	2.70	1.8	62	33	266	0.75	60	0.10
55	2.95	2.4	62	34	265	0.82	66	0.11

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 14 - Non-Recovery Males

DOSE LEVEL: 600 mg/kg/day

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
61	33	171	6.58	3.96	1.51	150	4.33	105
62	33	173	6.50	3.77	1.38	149	4.52	105
63	32	138	7.03	4.15	1.44	147	4.48	101
64	39	175	6.72	4.03	1.50	149	4.72	103
65	33	157	6.94	4.19	1.52	151	4.12	106

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
61	2.57	2.4	80	54	408	0.87	58	0.09
62	2.66	2.3	90	53	324	0.87	55	0.14
63	2.93	2.4	74	41	315	0.92	65	0.12
64	2.72	2.5	69	41	378	0.88	74	0.15
65	2.99	2.5	69	35	448	0.86	79	0.07

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 14 - Non-Recovery Females

DOSE LEVEL: 600 mg/kg/day

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
71	26	121	6.54	4.06	1.64	147	4.18	101
72	25	140	6.33	3.97	1.68	147	4.19	103
73	30	124	7.23	4.16	1.36	145	4.88	102
74	26	154	6.90	4.25	1.60	145	4.93	100
75	19	152	6.90	4.27	1.62	145	4.68	103

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
71	2.79	2.7	68	41	178	0.90	71	0.04
72	2.64	2.2	75	30	272	0.82	83	0.17
73	2.71	2.5	78	25	234	0.76	86	0.06
74	2.91	2.4	59	36	312	0.86	132	0.09
75	2.72	2.0	60	25	188	0.82	88	0.09

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 42 - Non-Recovery Males

DOSE LEVEL: 0 (Control)

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
1	34	187	6.54	3.81	1.40	148	4.54	105
2	26	172	6.92	3.69	1.14	146	4.51	103
3	33	162	6.24	3.52	1.29	148	4.82	105
4	29	148	7.39	3.74	1.02	146	4.36	103
5	28	156	6.48	3.54	1.20	146	4.72	104

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
1	2.80	1.8	61	40	294	0.78	79	0.25
2	2.63	1.8	81	41	275	0.82	62	0.18
3	2.29	1.8	76	43	309	0.80	45	0.20
4	2.65	2.5	81	38	432	0.81	74	0.28
5	2.54	1.5	72	40	232	0.74	69	0.21

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 5 *post partum* - Non-Recovery Females

DOSE LEVEL: 0 (Control)

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
11	45	109	5.38	2.95	1.21	148	4.93	102
12	54	141	5.64	3.37	1.48	148	4.88	103
13	44	133	5.25	2.98	1.31	150	5.56	103
14	30	163	6.22	3.31	1.14	147	5.13	101
15	35	129	5.53	3.27	1.45	149	5.02	103

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
11	2.58	1.7	89	66	187	0.69	62	0.02
12	2.41	1.2	95	87	221	0.80	57	0.01
13	2.59	2.0	104	47	206	0.98	46	0.10
14	2.50	1.6	68	69	99	0.82	54	0.00
15	2.46	2.2	61	51	204	0.63	55	0.00

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 42 - Non- Recovery Males

DOSE LEVEL: 50 mg/kg/day

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
21	26	140	6.89	3.70	1.16	146	4.54	104
22	31	139	6.66	3.64	1.21	147	4.87	104
23	30	165	6.83	3.43	1.01	145	4.47	102
24	33	177	6.51	3.66	1.28	148	4.77	105
25	25	153	6.36	3.44	1.18	148	4.25	106

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
21	2.36	2.2	83	53	369	0.75	60	0.23
22	2.68	1.9	72	47	365	0.81	81	0.23
23	1.89	1.8	86	43	290	0.87	53	0.17
24	2.60	2.0	60	39	264	0.80	74	0.19
25	2.48	1.5	71	39	383	0.73	53	0.16

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 5 *post partum* - Non- Recovery Females

DOSE LEVEL: 50 mg/kg/day

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
31	38	121	5.38	2.96	1.22	150	5.16	104
32	46	135	5.78	3.24	1.28	149	5.45	103
33	55	142	5.83	3.32	1.32	149	4.79	104
34	44	127	6.16	3.34	1.18	149	5.55	105
35	47	131	5.63	3.37	1.49	151	5.48	105

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
31	2.68	1.4	68	52	101	0.77	69	0.03
32	2.56	1.9	75	68	218	0.79	77	0.02
33	2.61	0.7	96	89	185	0.86	76	0.04
34	2.73	2.2	68	95	237	0.83	68	0.07
35	2.73	1.9	196	151	575	0.79	71	0.04

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 42 - Non-Recovery Males

DOSE LEVEL: 175 mg/kg/day

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
41	31	163	7.05	3.71	1.11	149	4.96	103
42	35	161	7.52	4.07	1.18	146	5.14	101
43	30	159	7.53	3.81	1.02	147	5.13	101
44	22	150	7.25	3.93	1.18	146	5.44	102
45	25	140	7.31	3.46	0.90	146	4.57	102

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
41	2.70	2.2	68	41	350	0.87	50	0.18
42	2.48	2.5	69	54	350	0.81	88	0.13
43	2.78	2.0	63	40	220	0.91	76	0.19
44	2.52	2.2	79	43	293	0.81	65	0.06
45	2.57	2.2	57	37	297	0.81	67	0.20

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 5 *post partum* - Non-Recovery Females

DOSE LEVEL: 175 mg/kg/day

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
51	33	121	5.60	3.27	1.40	152	4.64	107
52	62	133	5.95	3.46	1.39	148	4.08	103
53	39	138	6.06	3.16	1.09	146	5.37	102
54	42	109	5.75	3.03	1.11	150	4.58	105
55	40	116	5.85	3.10	1.13	151	6.37	102

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
51	2.45	1.4	138	143	176	0.80	67	0.04
52	2.44	1.2	52	93	223	1.16	77	0.07
53	2.32	1.3	56	64	289	0.61	56	0.07
54	2.56	1.8	103	68	196	0.83	60	0.07
55	2.45	2.1	87	82	156	0.68	49	0.00

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 42 - Non-Recovery Males

DOSE LEVEL: 600 mg/kg/day

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
61	24	155	6.83	3.80	1.25	146	4.91	101
62	29	144	6.36	3.56	1.27	147	4.84	104
63	25	141	7.39	3.79	1.05	145	4.53	102
64	31	143	6.86	3.85	1.28	146	4.94	101
65	28	135	6.88	3.82	1.25	146	4.96	103

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
61	2.71	2.2	85	53	324	0.87	63	0.31
62	2.47	1.9	87	50	234	0.84	31	0.18
63	2.70	1.8	79	32	247	0.87	72	0.27
64	2.67	2.2	72	33	378	0.87	66	0.21
65	2.62	2.2	66	30	336	0.81	84	0.29

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 5 *post partum* - Non-Recovery Females

DOSE LEVEL: 600 mg/kg/day

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
71	47	119	6.12	3.36	1.22	152	5.15	103
72	25	123	5.58	3.36	1.51	151	4.41	107
73	38	123	5.61	3.21	1.34	147	4.64	101
74	39	141	5.91	3.40	1.35	152	5.13	107
75	38	129	5.69	3.46	1.55	149	5.32	105

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
71	2.60	1.8	92	81	136	0.83	66	0.11
72	2.50	1.7	89	72	211	0.81	73	0.15
73	2.45	1.6	108	80	129	0.78	61	0.02
74	2.42	1.7	95	80	250	0.78	85	0.06
75	2.63	1.2	63	46	82	0.81	56	0.13

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 56 - Recovery Males

DOSE LEVEL: 0 (Control) Recovery

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
81	34	153	6.84	3.63	1.13	148	5.72	103
82	28	142	6.81	3.30	0.94	146	4.96	103
83	39	147	6.82	3.58	1.10	145	5.28	101
84	32	134	6.36	3.44	1.18	146	4.97	102
85	32	143	6.35	3.53	1.25	149	5.49	104

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
81	2.64	2.2	86	40	385	0.84	62	0.14
82	2.69	2.1	93	51	365	0.78	63	0.06
83	2.69	2.1	84	53	345	0.80	67	0.13
84	2.51	2.2	80	41	349	0.80	49	0.10
85	2.58	2.1	92	41	332	0.80	67	0.00

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 56 - Recovery Females

DOSE LEVEL: 0 (Control) Recovery

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
86	39	155	6.22	3.63	1.40	147	5.36	100
87	38	160	7.10	4.00	1.29	145	5.22	103
88	41	147	7.28	4.11	1.30	149	5.38	104
89	52	147	7.48	3.95	1.12	146	4.83	102
90	40	144	7.11	3.95	1.25	147	4.95	102

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
86	2.20	2.1	103	36	140	0.81	76	0.13
87	2.69	1.7	91	40	147	0.89	54	0.10
88	2.56	1.6	111	39	121	0.94	77	0.12
89	2.70	1.9	77	38	307	0.90	57	0.13
90	2.79	2.0	90	41	179	0.91	75	0.12

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 56 - Recovery Males

DOSE LEVEL: 600 mg/kg/day Recovery

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
91	41	149	7.20	3.93	1.20	150	5.08	102
92	43	133	7.28	3.91	1.16	148	5.63	102
93	40	146	7.71	3.99	1.07	146	5.34	100
94	30	141	7.40	4.01	1.18	149	5.51	101
95	46	136	7.58	3.76	0.98	146	5.79	101

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
91	2.61	2.2	91	42	341	0.86	67	0.08
92	2.14	2.1	75	44	205	0.78	74	0.11
93	2.78	2.2	80	48	420	0.82	81	0.11
94	2.82	2.4	80	45	274	0.83	90	0.14
95	2.68	2.1	72	36	182	0.85	75	0.14

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 9 (continued) Blood Chemistry - Individual Values

Day 56 - Recovery Females

DOSE LEVEL: 600 mg/kg/day Recovery

Animal Number	Urea (mg/dl)	Glucose (mg/dl)	Tot. Prot. (g/dl)	Albumin (g/dl)	A/G ratio	Na+ (mmol/l)	K+ (mmol/l)	Cl^- (mmol/l)
96	40	148	8.00	4.52	1.30	149	4.67	102
97	41	133	7.27	4.41	1.54	148	5.13	101
98	32	165	8.59	4.79	1.26	146	4.41	101
99	49	148	7.81	4.51	1.37	147	4.88	102
100	52	148	7.64	4.37	1.34	146	4.81	103

Animal Number	Ca++ (mmol/l)	P (mmol/l)	ASAT (IU/l)	ALAT (IU/l)	AP (IU/l)	Creat (mg/dl)	Chol (mg/dl)	Bili (mg/dl)
96	2.66	2.0	98	52	138	0.98	89	0.12
97	2.90	2.2	98	45	209	0.90	72	0.15
98	2.86	1.9	84	49	139	0.97	97	0.10
99	2.77	1.8	92	50	167	0.96	83	0.15
100	2.73	1.1	92	40	256	0.98	70	0.14

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 10 Urinalytical Findings - Individual Values

Dose Level (mg/kg/day)	Animal Number and Sex	Volume (ml)	Specific Gravity	pH	Protein	Glucose	Ketones
0 (Control)	1 M	6.0	1.041	6	1+	Normal	1+
	2 M	39.0	1.011	6	1+	Normal	Negative
	3 M	13.0	1.026	7	1+	Normal	1+
	4 M	17.0	1.022	7	1+	Normal	1+
	5 M	20.5	1.014	7	1+	Normal	Negative
Mean		19.1	1.023				
Standard Deviation		12.4	0.012				

Protein: 1+ = 0.3 g/l Ketones: 1+ = positive result

Dose Level (mg/kg/day)	Animal Number and Sex	Urobilinogen	Bilirubin	Blood	Reducing Substances (%)	Appearance
0 (Control)	1 M	Normal	Negative	Negative	0	NAD
	2 M	Normal	Negative	Negative	0.25	NAD
	3 M	Normal	Negative	Negative	0	NAD
	4 M	Normal	Negative	Negative	0	NAD
	5 M	Normal	Negative	Negative	0	NAD

Appearance: NAD = no abnormalities detected

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 10 (continued) Urinalytical Findings - Individual Values

Dose Level (mg/kg/day)	Animal Number and Sex	Volume (ml)	Specific Gravity	pH	Protein	Glucose	Ketones
50	21 M	10.5	1.025	6	1+	Normal	1+
	22 M	16.5	1.018	7	1+	Normal	1+
	23 M	15.0	1.019	6	1+	Normal	1+
	24 M	37.0	1.013	7	0	Normal	1+
	25 M	24.0	1.015	7	1+	Normal	1+
Mean		20.6	1.018				
Standard Deviation		10.4	0.005				

Protein: 0 = Negative
1+ = 0.3 g/l

Ketones: 1+ = positive result

Dose Level (mg/kg/day)	Animal Number and Sex	Urobilinogen	Bilirubin	Blood	Reducing Substances (%)	Appearance
50	21 M	Normal	Negative	Negative	0	NAD
	22 M	Normal	Negative	Negative	0	NAD
	23 M	Normal	Negative	Negative	0	NAD
	24 M	Normal	Negative	Negative	0	NAD
	25 M	Normal	Negative	Negative	0	NAD

Appearance: NAD = no abnormalities detected

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 10 (continued) Urinalytical Findings - Individual Values

Dose Level (mg/kg/day)	Animal Number and Sex	Volume (ml)	Specific Gravity	pH	Protein	Glucose	Ketones
175	41 M	21.0	1.022	7	1+	Normal	1+
	42 M	29.0	1.017	6	1+	Normal	1+
	43 M	26.0	1.016	7	0	Normal	1+
	44 M	33.5	1.013	7	0	Normal	1+
	45 M	29.5	1.011	7	1+	Normal	1+
Mean		27.8	1.016				
Standard Deviation		4.6	0.004				

Protein: 0 = negative
1+ = 0.3 g/l

Ketones: 1+ = positive result

Dose Level (mg/kg/day)	Animal Number and Sex	Urobilinogen	Bilirubin	Blood	Reducing Substances (%)	Appearance
175	41 M	Normal	Negative	Negative	0	NAD
	42 M	Normal	Negative	Negative	0	NAD
	43 M	Normal	Negative	Negative	0	NAD
	44 M	Normal	Negative	Negative	0	NAD
	45 M	Normal	Negative	Negative	0	NAD

Appearance: NAD = no abnormalities detected

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 10 (continued) Urinalytical Findings - Individual Values

Dose Level (mg/kg/day)	Animal Number and Sex	Volume (ml)	Specific Gravity	pH	Protein	Glucose	Ketones
600	61 M	10.0	1.024	6	1+	Normal	1+
	62 M	37.5	1.017	7	1+	Normal	1+
	63 M	19.5	1.023	6	1+	Normal	1+
	64 M	45.0	1.015	7	0	Normal	1+
	65 M	11.0	1.034	6	1+	Normal	1+
Mean		24.6	1.023				
Standard Deviation		15.9	0.007				

Protein: 0 = Negative
1+ = 0.3 g/l

Ketones: 1+ = positive result

Dose Level (mg/kg/day)	Animal Number and Sex	Urobilinogen	Bilirubin	Blood	Reducing Substances (%)	Appearance
600	61 M	Normal	Negative	Negative	0	NAD
	62 M	Normal	Negative	Negative	0	NAD
	63 M	Normal	Negative	Negative	0	NAD
	64 M	Normal	Negative	Negative	0	NAD
	65 M	Normal	Negative	Negative	0	NAD

Appearance: NAD = no abnormalities detected

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 10 (continued) Urinalytical Findings Individual - Values

Dose Level (mg/kg/day)	Animal Number and Sex	Volume (ml)	Specific Gravity	pH	Protein	Glucose	Ketones
0 (Control) Recovery Group	81 M	11.0	1.025	7	1+	Normal	1+
	82 M	6.0	1.042	6	1+	Normal	1+
	83 M	11.0	1.032	7	1+	Normal	1+
	84 M	12.5	1.027	7	1+	Normal	1+
	85 M	25.5	1.014	8	1+	Normal	1+
Mean		13.2	1.028				
Standard Deviation		7.3	0.010				

Protein: 1+ = 0.3 g/l Ketones: 1+ = positive result

Dose Level (mg/kg/day)	Animal Number and Sex	Urobilinogen	Bilirubin	Blood	Reducing Substances (%)	Appearance
0 (Control) Recovery Group	81 M	Normal	Negative	Negative	0	NAD
	82 M	Normal	Negative	Negative	0	NAD
	83 M	Normal	Negative	Negative	0	NAD
	84 M	Normal	Negative	Negative	0	NAD
	85 M	Normal	Negative	Negative	0	NAD

Appearance: NAD = no abnormalities detected

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 10 (continued) Urinalytical Findings - Individual Values

Dose Level (mg/kg/day)	Animal Number and Sex	Volume (ml)	Specific Gravity	pH	Protein	Glucose	Ketones
600 Recovery Group	91 M	9.5	1.033	7	1+	Normal	1+
	92 M	12.0	1.025	7	1+	Normal	1+
	93 M	10.5	1.023	8	1+	Normal	1+
	94 M	5.0	1.038	6	1+	Normal	1+
	95 M	6.0	1.043	7	1+	Normal	1+
Mean		8.6	1.032				
Standard Deviation		3.0	0.008				

Protein: 1+ = 0.3 g/l Ketones: 1+ = positive result

Dose Level (mg/kg/day)	Animal Number and Sex	Urobilinogen	Bilirubin	Blood	Reducing Substances (%)	Appearance
600 Recovery Group	91 M	Normal	Negative	1+	0	NAD
	92 M	Normal	Negative	1+	0.25	NAD
	93 M	Normal	Negative	1+	0.25	NAD
	94 M	Normal	Negative	0	0	NAD
	95 M	Normal	Negative	2+	0	NAD

Blood [haemoglobin]: 1+ = ca 10 Ery/µl
2+ = ca 25 Ery/µl

Appearance: NAD = no abnormalities detected

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 11 Mating Performance, Fertility and Gestation Length - Individual Values

DOSE LEVEL: 0 (Control)

Mated Animal Number		Pre-Coital Interval (Days)	Copulation Plug Count	Sperm Reading Score	Pregnancy Status	Gestation Length (Days)
11 F	1 M	2	4 PT H	2+	P	22
12 F	2 M	4	5 PT H	2+	P	23
13 F	3 M	2	3 PT H	2+	P	23
14 F	4 M	1	1 PT	1+	P	22½
15 F	5 M	1	3 PT H	2+	P	23
16 F	6 M	2	3 PT	2+	P	22
17 F	7 M	2	3 PT	2+	P	22
18 F	8 M	3	1 PT	2+	P	22
19 F	9 M	1	2 PT H	3+	P	23
20 F	10 M	1	4 PT H	3+	P	22

1+ = few spermatozoa present
2+ = continuous few spermatozoa in all fields
3+ = many spermatozoa in all fields
H = haemorrhage
P = pregnant
M = male
F = female
PT = plug detected on tray liner

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 11 (continued) Mating Performance, Fertility and Gestation Length - Individual Values

DOSE LEVEL: 50 mg/kg/day

Mated Animal Number		Pre-Coital Interval (Days)	Copulation Plug Count	Sperm Reading Score	Pregnancy Status	Gestation Length (Days)
31 F	21 M	2	4 PT	2+	P	22
32 F	22 M	1	3 PT	3+	P	23
33 F	23 M	4	4 PT H	2+	P	23
34 F	24 M	1	3 PT H	1+	P	22
35 F	25 M	1	4 PT H PV	3+	P	23
36 F	26 M	1	4 PT H	3+	P	22½
37 F	27 M	2	3 PT H	2+	P	22
38 F	28 M	3	3 PT	2+	P	23
39 F	29 M	1	4 PT	3+	P	22½
40 F	30 M	2	3 PT	2+	NP	NP

1+ = few spermatozoa present
2+ = continuous few spermatozoa in all fields
3+ = many spermatozoa in all fields
H = haemorrhage
P = pregnant
NP = not pregnant
M = male
F = female
PT = plug detected on tray liner
PV = Vaginal Plug

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 11 (continued) Mating Performance, Fertility and Gestation Length - Individual Values

DOSE LEVEL: 175 mg/kg/day

Mated Animal Number		Pre-Coital Interval (Days)	Copulation Plug Count	Sperm Reading Score	Pregnancy Status	Gestation Length (Days)
51 F	41 M	2	2 PT	2+	P	23
52 F	42 M	4	3 PT	2+	P	23
53 F	43 M	1	4 PT	3+	P	23
54 F	44 M	2	2 PT	2+	P	23
55 F	45 M	1	4 PT H	3+	P	22
56 F	46 M	2	3 PT	2+	P	22½
57 F	47 M	2	4 PT H	2+	P	22½
58 F	48 M	1	4 PT PV	2+	P	22½
59 F	49 M	2	4 PT H	2+	P	22
60 F	50 M	2	4 PT	2+	P	22½

2+ = continuous few spermatozoa in all fields
3+ = many spermatozoa in all fields
H = haemorrhage
P = pregnant
M = male
F = female
PT = plug detected on tray liner
PV = Vaginal Plug

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 11 (continued) Mating Performance, Fertility and Gestation Length - Individual Values

DOSE LEVEL: 600 mg/kg/day

Mated Animal Number		Pre-Coital Interval (Days)	Copulation Plug Count	Sperm Reading Score	Pregnancy Status	Gestation Length (Days)
71 F	61 M	2	4 PT H	2+	P	23
72 F	62 M	2	4 PT	2+	P	22½
73 F	63 M	3	5 PT	2+	P	23
74 F	64 M	2	4 PT	2+	P	23
75 F	65 M	1	5 PT	3+	P	23
76 F	66 M	4	2 PT	2+	P	22½
77 F	67 M	2	2 PT	2+	P	23
78 F	68 M	2	4 PT H	2+	P	22½
79 F	69 M	3	3 PT	2+	P	22
80 F	70 M	4	4 PT	2+	P	23

2+ = continuous few spermatozoa in all fields
3+ = many spermatozoa in all fields
H = haemorrhage
P = pregnant
M = male
F = female
PT = plug detected on tray liner

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 12 Litter and Offspring Bodyweight Data - Individual Values

DOSE LEVEL: 0 (Control)

Animal/Litter Number	Number of Corpora Lutea	Number of Implantation Sites	Total number of Offspring Born	Number of Live Offspring		Litter Weight (g)		Offspring Weight (g)				Offspring Bodyweight Change (g)	
								Day 1		Day 4		Days 1 - 4	
				Day 1	Day 4	Day 1	Day 4	Males	Females	Males	Females	Males	Females
11	20	16	16	15	14	91.1	126.8	6.3	5.9	9.2	9.0	2.8	3.1
12	17	16	13	13	13	105.1	152.8	8.5	7.8	12.2	11.4	3.7	3.6
13	17	15	15	14	14	107.6	150.9	7.8	7.5	10.9	10.6	3.1	3.2
14	7	5	5	5	5	38.1	62.0	7.8	7.4	12.5	12.3	4.7	4.9
15 KIE	19	15	-	-	-	-	-	-	-	-	-	-	-
16	15	15	14	14	14	92.8	140.2	6.7	6.5	10.1	9.9	3.4	3.4
17	19	16	16	16	15	101.4	140.9	6.6	6.0	9.7	9.0	3.1	3.0
18	19	14	14	14	14	98.9	149.0	7.3	6.8	10.9	10.4	3.6	3.6
19	16	■	16	14	14	103.8	144.3	7.6	7.3	10.7	9.9	3.2	2.6
20	18	15	14	14	14	98.8	155.3	7.4	6.7	11.5	10.7	4.0	4.1

KIE = killed *in extremis*
■ = data unavailable

Appendix 12 (continued) Litter and Offspring Bodyweight Data - Individual Values

DOSE LEVEL: 50 mg/kg/day

Animal/Litter Number	Number of Corpora Lutea	Number of Implantation Sites	Total number of Offspring Born	Number of Live Offspring		Litter Weight (g)		Offspring Weight (g)				Offspring Bodyweight Change (g)	
								Day 1		Day 4		Days 1- 4	
				Day 1	Day 4	Day 1	Day 4	Males	Females	Males	Females	Males	Females
31	18	15	13	12	12	75.1	121.8	6.4	6.0	10.3	9.9	3.9	3.9
32	14	14	14	14	14	101.2	140.0	7.4	7.2	9.9	10.0	2.5	2.9
33	17	15	14	13	13	98.4	140.8	7.7	7.6	11.4	10.8	3.7	3.2
34	19	18	17	16	16	111.3	179.5	7.1	6.7	11.5	10.9	4.4	4.1
35	15	15	14	14	14	99.2	150.1	7.1	7.1	10.5	10.8	3.4	3.8
36	12	■	12	12	12	92.9	143.1	7.8	7.6	12.1	11.5	4.3	3.9
37	16	15	15	14	14	81.4	121.8	5.9	5.8	8.6	8.8	2.7	3.0
38	17	17	15	15	15	101.3	146.5	6.8	6.4	9.9	9.3	3.0	2.9
39	20	17	17	17	17	120.6	172.8	7.3	6.9	10.6	9.8	3.3	2.9
40 NP													

■ = data unavailable
NP = not pregnant

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 12 (continued) Litter and Offspring Bodyweight Data - Individual Values

DOSE LEVEL: 175 mg/kg/day

Animal/Litter Number	Number of Corpora Lutea	Number of Implantation Sites	Total number of Offspring Born	Number of Live Offspring		Litter Weight (g)		Offspring Weight (g)				Offspring Bodyweight Change (g)	
								Day 1		Day 4		Days 1- 4	
				Day 1	Day 4	Day 1	Day 4	Males	Females	Males	Females	Males	Females
51	21	16	15	15	15	119.9	184.8	8.3	7.7	12.6	12.0	4.4	4.3
52	14	14	13	12	12	83.7	130.5	7.5	6.8	11.5	10.7	4.0	3.9
53	15	15	13	13	13	93.5	142.9	7.4	7.1	11.3	10.9	3.9	3.8
54	17	15	13	13	13	113.1	160.7	8.8	8.6	12.4	12.3	3.7	3.7
55	17	16	15	15	15	97.7	144.4	6.8	6.3	9.8	9.5	3.0	3.2
56	21	16	14	14	14	94.7	148.5	6.9	6.4	10.8	10.3	3.8	3.9
57	18	16	15	14	14	92.5	142.9	6.8	6.5	10.7	9.9	3.9	3.4
58	16	16	16	16	16	109.9	170.2	7.2	6.6	11.2	10.2	4.0	3.6
59	16	15	14	14	14	82.4	123.8	6.0	5.7	9.0	8.5	3.0	2.8
60	15	15	15	15	15	97.6	145.8	6.7	6.2	10.0	9.4	3.3	3.1

Appendix 12 (continued) Litter and Offspring Bodyweight Data - Individual Values

DOSE LEVEL: 600 mg/kg/day

Animal/Litter Number	Number of Corpora Lutea	Number of Implantation Sites	Total number of Offspring Born	Number of Live Offspring		Litter Weight (g)		Offspring Weight (g)				Offspring Bodyweight Change (g)	
								Day 1		Day 4		Days 1- 4	
				Day 1	Day 4	Day 1	Day 4	Males	Females	Males	Females	Males	Females
71	19	16	13	13	13	89.5	124.6	7.1	6.7	9.8	9.4	2.7	2.7
72	14	12	12	12	12	74.4	106.3	6.5	6.1	9.4	8.8	2.9	2.6
73	19	12	11	11	11	70.9	94.7	6.8	6.3	8.8	8.5	2.0	2.2
74	21	18	17	14	13	72.1	97.0	5.3	5.1	7.7	7.4	2.4	2.3
75	20	16	15	14	13	78.3	109.5	5.8	5.4	8.7	8.1	2.9	2.8
76	19	18	16	15	15	88.9	119.8	6.1	5.7	8.2	7.7	2.1	2.0
77	19	12	12	12	12	96.7	127.5	8.2	8.0	10.4	10.9	2.2	2.9
78	13	13	13	13	13	85.9	128.3	6.9	6.4	10.2	9.6	3.3	3.2
79	18	18	16	15	15	77.3	111.8	5.4	5.0	7.9	7.2	2.5	2.2
80	16	15	13	13	13	95.0	137.5	7.5	7.0	10.9	10.1	3.4	3.1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 13 Implantation Losses and Survival Indices - Individual Litter Values

DOSE LEVEL: 0 (Control)

Litter Number	Pre-Implantation Loss (%)	Post-Implantation Loss (%)	Live Birth Index	Viability Index
11	20	0	94	93
12	6	19	100	100
13	12	0	93	100
14	29	0	100	100
15 KIE				
16	0	7	100	100
17	16	0	100	94
18	26	0	100	100
19	-	-	88	100
20	17	7	100	100

KIE = killed *in extremis*
- = data unavailable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 13 (continued) Implantation Losses and Survival Indices - Individual Litter Values

DOSE LEVEL: 50 mg/kg/day

Litter Number	Pre-Implantation Loss (%)	Post-Implantation Loss (%)	Live Birth Index	Viability Index
31	17	13	92	100
32	0	0	100	100
33	12	7	93	100
34	5	6	94	100
35	0	7	100	100
36	■	■	100	100
37	6	0	93	100
38	0	12	100	100
39	15	0	100	100
40 NP				

■ = data unavailable
NP = not pregnant

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 13 (continued) Implantation Losses and Survival Indices - Individual Litter Values

DOSE LEVEL: 175 mg/kg/day

Litter Number	Pre- Implantation Loss (%)	Post -Implantation Loss (%)	Live Birth Index	Viability Index
51	24	6	100	100
52	0	7	92	100
53	0	13	100	100
54	12	13	100	100
55	6	6	100	100
56	24	13	100	100
57	11	6	93	100
58	0	0	100	100
59	6	7	100	100
60	0	0	100	100

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 13 (continued) Implantation Losses and Survival Indices - Individual litter values

DOSE LEVEL: 600 mg/kg/day

Litter Number	Pre- Implantation Loss (%)	Post -Implantation Loss (%)	Live Birth Index	Viability Index
71	16	19	100	100
72	14	0	100	100
73	37	8	100	100
74	14	6	82	93
75	20	6	93	93
76	5	11	94	100
77	37	0	100	100
78	0	0	100	100
79	0	11	94	100
80	6	13	100	100

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 14 Sex ratio - Individual Litter Values

DOSE LEVEL: 0 (Control)

Litter Number	Sex Ratio (*Post Partum*) Day:								
	At birth			1			4		
	Male	Female	% Male	Male	Female	% Male	Male	Female	% Male
11 †	7	8	47	7	8	47	7	7	50
12	6	7	46	6	7	46	6	7	46
13	10	5	67	9	5	64	9	5	64
14	3	2	60	3	2	60	3	2	60
15 KIE									
16	7	7	50	7	7	50	7	7	50
17	10	6	63	10	6	63	9	6	60
18	8	6	57	8	6	57	8	6	57
19 †	8	7	53	7	7	50	7	7	50
20	7	7	50	7	7	50	7	7	50

KIE = killed *in extremis*
† = values do not include one offspring that was missing between pre-day 1 and Day 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 14 (continued) Sex Ratio - Individual Litter Values

DOSE LEVEL: 50 mg/kg/day

Litter Number	Sex Ratio (*Post Partum*) Day:								
	At birth			1			4		
	Male	Female	% Male	Male	Female	% Male	Male	Female	% Male
31	8	4	67	8	4	67	8	4	67
32	4	10	29	4	10	29	4	10	29
33 †	1	12	8	1	12	8	1	12	8
34	9	8	53	9	7	56	9	7	56
35	5	9	36	5	9	36	5	9	36
36	8	4	67	8	4	67	8	4	67
37 †	6	8	43	6	8	43	6	8	43
38	12	3	80	12	3	80	12	3	80
39	8	9	47	8	9	47	8	9	47
40 NP									

NP = not pregnant
† = values do not include one offspring that was missing between pre-day 1 and Day 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 14 (continued) Sex Ratio - Individual Litter Values

DOSE LEVEL: 175 mg/kg/day

Litter Number	Sex Ratio (*Post Partum*) Day:								
	At birth			1			4		
	Male	Female	% Male	Male	Female	% Male	Male	Female	% Male
51	8	7	53	8	7	53	8	7	53
52 †	3	9	25	3	9	25	3	9	25
53	4	9	31	4	9	31	4	9	31
54	6	7	46	6	7	46	6	7	46
55	6	9	40	6	9	40	6	9	40
56	9	5	64	9	5	64	9	5	64
57 †	6	8	43	6	8	43	6	8	43
58	6	10	38	6	10	38	6	10	38
59	9	5	64	9	5	64	9	5	64
60	9	6	60	9	6	60	9	6	60

† = values do not include one offspring that was missing between pre-day 1 and Day 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 14 (continued) Sex Ratio - Individual Litter Values

DOSE LEVEL: 600 mg/kg/day

Litter Number	Sex Ratio (*Post Partum*) Day:								
	At birth			1			4		
	Male	Female	% Male	Male	Female	% Male	Male	Female	% Male
71	6	7	46	6	7	46	6	7	46
72	2	10	17	2	10	17	2	10	17
73	3	8	27	3	8	27	3	8	27
74 †	6	9	40	5	9	36	4	9	31
75 †	8	6	57	8	6	57	7	6	54
76	9	7	56	9	6	60	9	6	60
77	6	6	50	6	6	50	6	6	50
78	6	7	46	6	7	46	6	7	46
79 †	6	9	40	6	9	40	6	9	40
80	8	5	62	8	5	62	8	5	62

† = values do not include offspring that was found dead and/or missing between pre-day 1 and Day 1

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 15 Clinical Signs - Individual Litter Observations

DOSE LEVEL: 0 (Control)

Litter Number	Offspring Affected	Clinical Observation	Day *post partum*
11	F15 F15 Remaining litter	Small Missing NAD	1 2 1-5
12	Whole litter	NAD	1-5
13	Whole litter	NAD	1-5
14	Whole litter	NAD	1-5
15 KIE	-	-	-
16	Whole litter	NAD	1-5
17	M18 Remaining litter	Found dead NAD	2 1-5
18	M1 Remaining litter	Bruise on snout NAD	PD1 – 1 1-5
19	1* Remaining litter	Missing NAD	1 1-5
20	Whole litter	NAD	1-5

M = male
F = female
NAD = No Abnormalities Detected
KIE = killed *in extremis*
- = not applicable
PD1 = pre-day 1
* = sex undetermined

Appendix 15 (continued) Clinical Signs - Individual Litter Observations

DOSE LEVEL: 50 mg/kg/day

Litter Number	Offspring Affected	Clinical Observation	Day *post partum*
31	1F 1* Remaining litter	Bruising on head Missing NAD	PD1 1 1-5
32	Whole litter	NAD	1-5
33	1* Remaining litter	Missing NAD	1 1-5
34	Whole litter	NAD	1-5
35	Whole litter	NAD	1-5
36	Whole litter	NAD	1-5
37	1* F14 F14 Remaining litter	Missing Small Wound on back NAD	1 1 1, 4, 5 1-5
38	Whole litter	NAD	1-5
39	Whole litter	NAD	1-5
40 NP	-	-	-

F = female
PD1 = pre-day 1
NAD = No Abnormalities Detected
NP = Not pregnant
* = sex undetermined
- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 15 (continued) Clinical Signs - Individual Litter Observations

DOSE LEVEL: 175 mg/kg/day

Litter Number	Number and sex of Offspring Affected	Clinical Observation	Day *post partum*
51	Whole litter	NAD	1-5
52	1* Remaining litter	Missing NAD	1 1-5
53	Whole litter	NAD	1-5
54	Whole litter	NAD	1-5
55	Whole litter	NAD	1-5
56	Whole litter	NAD	1-5
57	1* F8, F9 Remaining litter	Missing Found dead NAD	1 5 1-5
58	Whole litter	NAD	1-5
59	1F Remaining litter	Weak NAD	PD1 1-5
60	Whole litter	NAD	1-5

PD1 = pre-day 1
F = female
NAD = No Abnormalities Detected
* = sex undetermined

Appendix 15 (continued) Clinical Signs - Individual Litter Observations

DOSE LEVEL: 600 mg/kg/day

Litter Number	Number and sex of Offspring Affected	Clinical Observation	Day *post partum*
71	F9 Remaining litter	Atrietic tail No tail NAD	PD1 - 4 5 1-5
72	F5 Remaining litter	Missing NAD	5 1-5
73	Whole litter	NAD	1-5
74	1M 1* M1 Remaining litter	Found dead Missing Found dead NAD	1 1 2 1-5
75	1* M1 Remaining litter	Missing Found dead NAD	1 4 1-5
76	Whole litter	NAD	1-5
77	M3 F11 Remaining litter	Small Cut on nose NAD	1-5 3-5 1-5
78	Whole litter	NAD	1-5
79	1* Remaining litter	Missing NAD	1 1-5
80	Whole litter	NAD	1-5

PD1

M = male
F = female
NAD = No Abnormalities Detected
PD1 = pre-day 1
* = sex undetermined

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 16 Offspring Reflexological Responses - Individual Values

DOSE LEVEL: 0 (Control)

Litter Number	Surface Righting Reflex		
	Number of Offspring Examined	Number of Offspring Passed	% Passed
11	15	12	80.0
12	13	11	84.6
13	14	14	100.0
14	5	4	80.0
15 KIE			
16	14	14	100.0
17	16	14	87.5
18	14	12	85.7
19	14	14	100.0
20	14	12	85.7

KIE = killed *in extremis*

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 16 (continued) Offspring Reflexological Responses - Individual Values

DOSE LEVEL: 50 mg/kg/day

Litter Number	Surface Righting Reflex		
	Number of Offspring Examined	Number of Offspring Passed	% Passed
31	12	9	75.0
32	14	14	100.0
33	13	12	92.3
34	16	15	93.8
35	14	14	100.0
36	12	11	91.7
37	14	14	100.0
38	15	14	93.3
39	17	17	100.0
40 NP			

NP = not pregnant

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 16 (continued) Offspring Reflexological Responses - Individual Values

DOSE LEVEL: 175 mg/kg/day

Litter Number	Surface Righting Reflex		
	Number of Offspring Examined	Number of Offspring Passed	% Passed
51	15	14	93.3
52	12	12	100.0
53	13	13	100.0
54	13	13	100.0
55	15	15	100.0
56	14	14	100.0
57	14	14	100.0
58	16	15	93.8
59	14	14	100.0
60	15	14	93.3

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 16 (continued) Offspring Reflexological Responses - Individual Values

DOSE LEVEL: 600 mg/kg/day

Litter Number	Surface Righting Reflex		
	Number of Offspring Examined	Number of Offspring Passed	% Passed
71	13	13	100.0
72	12	10	83.3
73	11	11	100.0
74	14	13	92.9
75	14	14	100.0
76	15	14	93.3
77	12	12	100.0
78	13	13	100.0
79	15	14	93.3
80	13	13	100.0

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 17 Necropsy Findings of Offspring - Individual Observations

DOSE LEVEL: 0 (Control)

Litter Number	Interim Deaths			Terminal kill Day 5 *Post Partum*	
	Necropsy Day (*Post Partum*):	Offspring Number	Macroscopic Observation	Offspring Number	Macroscopic Observation
11	-	-	-	Whole litter	No abnormalities detected
12	-	-	-	Whole litter	No abnormalities detected
13	PD1	1M*	No abnormalities detected	Whole litter	No abnormalities detected
14	-	-	-	Whole litter	No abnormalities detected
15 KIE	-	-	-	-	-
16	-	-	-	Whole litter	No abnormalities detected
17	2	8M	Autolysis	Whole litter	No abnormalities detected
18	-	-	-	Whole litter	No abnormalities detected
19	PD1	1M*	Autolysis	Whole litter	No abnormalities detected
20	-	-	-	Whole litter	No abnormalities detected

M = male
KIE = killed *in extremis*
PD1 = Pre-Day 1
- = not applicable
* = sex determined internally, animal had not yet been individually identified

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 17 (continued) Necropsy Findings of Offspring - Individual Observations

DOSE LEVEL: 50 mg/kg/day

Litter Number	Interim Deaths			Terminal kill Day 5 *Post Partum*	
	Necropsy Day (*Post Partum*):	Offspring Number	Macroscopic Observation	Offspring Number	Macroscopic Observation
31	-	-	-	Whole litter	No abnormalities detected
32	-	-	-	Whole litter	No abnormalities detected
33	-	-	-	Whole litter	No abnormalities detected
34	PD1	1F*	Autolysis	Whole litter	No abnormalities detected
35	-	-	-	Whole litter	No abnormalities detected
36	-	-	-	Whole litter	No abnormalities detected
37	-	-	-	F14	Wound on back
				Remaining litter	No abnormalities detected
38	-	-	-	Whole litter	No abnormalities detected
39	-	-	-	F15	Mottled liver
				Remaining litter	No abnormalities detected
40 NP	-	-	-	-	-

F = female
NP = not pregnant
PD1 = Pre-Day 1
- = not applicable
* = sex determined internally, animal had not yet been individually identified

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 17 (continued) Necropsy Findings of Offspring - Individual Observations

DOSE LEVEL: 175 mg/kg/day

Litter Number	Interim Deaths			Terminal kill Day 5 *Post Partum*	
	Necropsy Day (*Post Partum*):	Offspring Number	Macroscopic Observation	Offspring Number	Macroscopic Observation
51	-	-	-	Whole litter	No abnormalities detected
52	-	-	-	Whole litter	No abnormalities detected
53	-	-	-	Whole litter	No abnormalities detected
54	-	-	-	Whole litter	No abnormalities detected
55	-	-	-	Whole litter	No abnormalities detected
56	-	-	-	Whole litter	No abnormalities detected
57	5	8F, 9F	Autolysis	Remaining litter	No abnormalities detected
58	-	-	-	Whole litter	No abnormalities detected
59	-	-	-	Whole litter	No abnormalities detected
60	-	-	-	Whole litter	No abnormalities detected

- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 17 (continued) Necropsy Findings of Offspring - Individual Observations

DOSE LEVEL: 600 mg/kg/day

Litter Number	Interim Deaths			Terminal kill Day 5 *Post Partum*	
	Necropsy Day (*Post Partum*):	Offspring Number	Macroscopic Observation	Offspring Number	Macroscopic Observation
71	-	-	-	F9	No tail
				Remaining litter	No abnormalities detected
72	-	-	-	Whole litter	No abnormalities detected
73	-	-	-	F4	Extra lobulation on right lung
				Remaining litter	No abnormalities detected
74	PD1	1M*	No abnormalities detected	Whole litter	No abnormalities detected
	1	1M*	No abnormalities detected		
	2	M1	Autolysis		
75	4	M1	No abnormalities detected	Whole litter	No abnormalities detected
76	PD1	1F*	Autolysis	Whole litter	No abnormalities detected
77	-	-	-	M3	Small
				F11	Cut on nose
				Remaining litter	No abnormalities detected
78	-	-	-	Whole litter	No abnormalities detected
79	-	-	-	Whole litter	No abnomalities detected
80	-	-	-	Whole litter	No abnormalities detected

M = male
F = female
PD1 = Pre-Day 1
- = not applicable
* = sex determined internally, animal had not yet been individually identified

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 18 Necropsy Findings of Adults - Individual Observations

Non-Recovery Males

DOSE LEVEL: 0 (Control)

Animal Number	Mode of Death	Macroscopic Observations
1	Terminal kill	No abnormalities detected
2	Terminal kill	No abnormalities detected
3	Terminal kill	No abnormalities detected
4	Terminal kill	No abnormalities detected
5	Terminal kill	No abnormalities detected
6	Terminal kill	No abnormalities detected
7	Terminal kill	No abnormalities detected
8	Terminal kill	No abnormalities detected
9	Terminal kill	No abnormalities detected
10	Terminal kill	No abnormalities detected

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 18 (continued) Necropsy Findings of Adults - Individual Observations

Non-Recovery Females

DOSE LEVEL: 0 (Control)

Animal Number	Mode of Death	Macroscopic Observations
11	Terminal kill	No abnormalities detected
12	Terminal kill	No abnormalities detected
13	Terminal kill	No abnormalities detected
14	Terminal kill	No abnormalities detected
15	Interim death	15 foetuses in uterus, 2 foetuses and placenti positioned close to bifurcation of uterine horns Adrenals: pale
16	Terminal kill	No abnormalities detected
17	Terminal kill	No abnormalities detected
18	Terminal kill	No abnormalities detected
19	Terminal kill	No abnormalities detected
20	Terminal kill	No abnormalities detected

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 18 (continued) Necropsy Findings of Adults - Individual observations

Non-Recovery Males

DOSE LEVEL: 50 mg/kg/day

Animal Number	Mode of death	Macroscopic Observations
21	Terminal kill	No abnormalities detected
22	Terminal kill	No abnormalities detected
23	Terminal kill	No abnormalities detected
24	Terminal kill	No abnormalities detected
25	Terminal kill	No abnormalities detected
26	Terminal kill	No abnormalities detected
27	Terminal kill	No abnormalities detected
28	Terminal kill	No abnormalities detected
29	Terminal kill	No abnormalities detected
30 S	Terminal kill	No abnormalities detected

S = failed to induce prenancy in female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 18 (continued) Necropsy Findings of Adults - Individual Observations

Non-Recovery Females

DOSE LEVEL: 50 mg/kg/day

Animal Number	Mode of Death	Macroscopic Observations
31	Terminal kill	No abnormalities detected
32	Terminal kill	No abnormalities detected
33	Terminal kill	No abnormalities detected
34	Terminal kill	No abnormalities detected
35	Terminal kill	No abnormalities detected
36	Terminal kill	**Uterus:** damaged on removal (unrelated to treatment)
37	Terminal kill	No abnormalities detected
38	Terminal kill	No abnormalities detected
39	Terminal kill	No abnormalities detected
40 NP	Terminal kill	No abnormalities detected

NP = not pregnant

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 18 (continued) Necropsy Findings of Adults - Individual Observations

Non-Recovery Males

DOSE LEVEL: 175 mg/kg/day

Animal Number	Mode of Death	Macroscopic Observations
41	Terminal kill	No abnormalities detected
42	Terminal kill	Kidneys: hydronephrosis
43	Terminal kill	No abnormalities detected
44	Terminal kill	No abnormalities detected
45	Terminal kill	No abnormalities detected
46	Terminal kill	No abnormalities detected
47	Terminal kill	No abnormalities detected
48	Terminal kill	No abnormalities detected
49	Terminal kill	No abnormalities detected
50	Terminal kill	No abnormalities detected

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 18 (continued) Necropsy Findings of Adults - Individual Observations

Non-Recovery Females

DOSE LEVEL: 175 mg/kg/day

Animal Number	Mode of Death	Macroscopic Observations
51	Terminal kill	No abnormalities detected
52	Terminal kill	No abnormalities detected
53	Terminal kill	No abnormalities detected
54	Terminal kill	Intestines: gaseous distension
55	Terminal kill	No abnormalities detected
56	Terminal kill	No abnormalities detected
57	Terminal kill	No abnormalities detected
58	Terminal kill	**Uterus:** damaged on removal (unrelated to treatment)
59	Terminal kill	No abnormalities detected
60	Terminal kill	No abnormalities detected

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 18 (continued) Necropsy Findings of Adults - Individual observations

Non-Recovery Males

DOSE LEVEL: 600 mg/kg/day

Animal Number	Mode of Death	Macroscopic Observations
61	Terminal kill	No abnormalities detected
62	Terminal kill	No abnormalities detected
63	Terminal kill	**Adrenal:** one lost after removal (unrelated to treatment)
64	Terminal kill	Left testes and epididymides: small
65	Terminal kill	No abnormalities detected
66	Terminal kill	No abnormalities detected
67	Terminal kill	**Left epididymide:** damaged on removal (unrelated to treatment)
68	Terminal kill	No abnormalities detected
69	Terminal kill	No abnormalities detected
70	Terminal kill	Bladder: filled with red fluid

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 18 (continued) Necropsy Findings of Adults - Individual observations

Non-Recovery Females

DOSE LEVEL: 600 mg/kg/day

Animal Number	Mode of death	Macroscopic Observations
71	Terminal kill	No abnormalities detected
72	Terminal kill	No abnormalities detected
73	Terminal kill	No abnormalities detected
74	Terminal kill	No abnormalities detected
75	Terminal kill	No abnormalities detected
76	Terminal kill	No abnormalities detected
77	Terminal kill	No abnormalities detected
78	Terminal kill	No abnormalities detected
79	Terminal kill	No abnormalities detected
80	Terminal kill	No abnormalities detected

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 18 (continued) Necropsy Findings of Adults - Individual Observations

Recovery Males

DOSE LEVEL: 0 (control) Recovery

Animal Number	Mode of Death	Macroscopic Observations
81	Terminal kill	No abnormalities detected
82	Terminal kill	No abnormalities detected
83	Terminal kill	No abnormalities detected
84	Terminal kill	No abnormalities detected
85	Terminal kill	No abnormalities detected

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 18 (continued) Necropsy Findings of Adults - Individual Observations

Recovery Females

DOSE LEVEL: 0 (control) Recovery

Animal Number	Mode of death	Macroscopic Observations
86	Terminal kill	No abnormalities detected
87	Terminal kill	No abnormalities detected
88	Terminal kill	No abnormalities detected
89	Terminal kill	No abnormalities detected
90	Terminal kill	No abnormalities detected

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 18 (continued) Necropsy Findings of Adults - Individual Observations

Recovery Males

DOSE LEVEL: 600 mg/kg/day Recovery

Animal Number	Mode of Death	Macroscopic Observations
91	Terminal kill	No abnormalities detected
92	Terminal kill	No abnormalities detected
93	Terminal kill	No abnormalities detected
94	Terminal kill	No abnormalities detected
95	Terminal kill	No abnormalities detected

Appendix 18 (continued) Necropsy Findings of Adults - Individual Observations

Recovery Females

DOSE LEVEL: 600 mg/kg/day Recovery

Animal Number	Mode of death	Macroscopic Observations
96	Terminal kill	No abnormalities detected
97	Terminal kill	No abnormalities detected
98	Terminal kill	No abnormalities detected
99	Terminal kill	No abnormalities detected
100	Terminal kill	No abnormalities detected

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 Absolute Organ Weights with Corresponding Relative Organ Weights (% of Bodyweight) - Individual Values

Non-Recovery Males

DOSE LEVEL: 0 (Control)

Animal Number	Bodyweight (g) at Terminal Kill	Organ Weight (g)								
		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Spleen	Testes	Thymus
1	489	0.0624	1.9815	1.3343	1.8556	3.5348	19.9546	0.6944	3.5118	0.5603
2	449	0.0484	2.0291	1.4318	1.3454	3.5018	15.2298	0.7092	3.7605	0.3976
3	457	0.0596	2.1835	1.3647	1.6058	3.5749	14.1482	0.7088	2.9770	0.3642
4	457	0.0644	2.0350	1.5772	1.8522	3.8499	16.3541	0.7511	3.5696	0.3088
5	410	0.0636	2.1020	1.2642	1.5992	3.2243	14.0880	0.8227	3.2509	0.4040
6	528	-	-	1.3156	-	-	-	-	3.6731	-
7	434	-	-	1.4804	-	-	-	-	3.6666	-
8	495	-	-	1.4191	-	-	-	-	3.8592	-
9	533	-	-	1.3627	-	-	-	-	3.7123	-
10	561	-	-	1.3994	-	-	-	-	3.5544	-

Animal Number	Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)								
		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Spleen	Testes	Thymus
1	489	0.0128	0.4052	0.2729	0.3795	0.7229	4.0807	0.1420	0.7182	0.1146
2	449	0.0108	0.4519	0.3189	0.2996	0.7799	3.3919	0.1580	0.8375	0.0886
3	457	0.0130	0.4778	0.2986	0.3514	0.7823	3.0959	0.1551	0.6514	0.0797
4	457	0.0141	0.4453	0.3451	0.4053	0.8424	3.5786	0.1644	0.7811	0.0676
5	410	0.0155	0.5127	0.3083	0.3900	0.7864	3.4361	0.2007	0.7929	0.0985
6	528	-	-	0.2492	-	-	-	-	0.6957	-
7	434	-	-	0.3411	-	-	-	-	0.8448	-
8	495	-	-	0.2867	-	-	-	-	0.7796	-
9	533	-	-	0.2557	-	-	-	-	0.6965	-
10	561	-	-	0.2494	-	-	-	-	0.6336	-

- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 (continued) Absolute Organ Weights with Corresponding Relative Organ Weights (% of Bodyweight) - Individual Values

Non-Recovery Females

DOSE LEVEL: 0 (Control)

Animal Number	Bodyweight (g) at Terminal Kill	Organ Weight (g)							
		Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus
11	273	0.0854	1.8062	1.0231	2.0147	12.8445	0.1133	0.4925	0.2601
12	319	0.0886	1.9662	1.1106	2.2650	14.8324	0.1853	0.6165	0.3544
13	298	0.0804	1.7539	1.1747	1.9263	12.0876	0.0824	0.5617	0.4256
14	327	0.0640	1.7795	0.9628	1.9787	14.0806	0.1383	0.6729	0.3953
15 KIE	-	-	-	-	-	-	-	-	-
16	336	0.1051	1.8216	1.1195	2.3052	14.1734	0.1369	0.6454	0.3359
17	317	-	-	-	-	-	0.1736	-	-
18	322	-	-	-	-	-	0.1375	-	-
19	330	-	-	-	-	-	0.1292	-	-
20	353	-	-	-	-	-	0.1199	-	-

Animal Number	Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)							
		Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus
11	273	0.0313	0.6616	0.3748	0.7380	4.7049	0.0415	0.1804	0.0953
12	319	0.0278	0.6164	0.3482	0.7100	4.6497	0.0581	0.1933	0.1111
13	298	0.0270	0.5886	0.3942	0.6464	4.0562	0.0277	0.1885	0.1428
14	327	0.0196	0.5442	0.2944	0.6051	4.3060	0.0423	0.2058	0.1209
15 KIE	-	-	-	-	-	-	-	-	-
16	336	0.0313	0.5421	0.3332	0.6861	4.2183	0.0407	0.1921	0.1000
17	317	-	-	-	-	-	0.0548	-	-
18	322	-	-	-	-	-	0.0427	-	-
19	330	-	-	-	-	-	0.0392	-	-
20	353	-	-	-	-	-	0.0340	-	-

KIE = animal killed *in extremis* during parturition
- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 (continued) Absolute Organ Weights with Corresponding Relative Organ Weights (% of Bodyweight) - Individual Values

Non-Recovery Males

DOSE LEVEL: 50 mg/kg/day

Animal Number	Bodyweight (g) at Terminal Kill	Organ Weight (g)								
		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Spleen	Testes	Thymus
21	422	0.0562	2.0221	1.2169	1.6474	3.2235	14.3127	0.6439	3.3610	0.2289
22	450	0.0503	2.0182	1.3708	1.8614	3.8162	15.4801	0.8156	3.4954	0.3614
23	410	0.0502	1.9504	1.3332	1.7506	2.9297	12.9306	0.6515	3.6681	0.3740
24	522	0.0617	1.9990	1.5064	1.5003	4.1636	18.3102	0.7649	3.7213	0.4336
25	472	0.0664	2.1420	1.1204	1.3760	3.6375	16.4362	0.8138	3.3349	0.4475
26	502	-	-	1.3874	-	-	-	-	3.5060	-
27	526	-	-	1.1851	-	-	-	-	3.5889	-
28	461	-	-	1.2651	-	-	-	-	3.1177	-
29	525	-	-	1.3276	-	-	-	-	3.0463	-
30	486	-	-	1.3917	-	-	-	-	3.9920	-

Animal Number	Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)								
		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Spleen	Testes	Thymus
21	422	0.0133	0.4792	0.2884	0.3904	0.7639	3.3916	0.1526	0.7964	0.0542
22	450	0.0112	0.4485	0.3046	0.4136	0.8480	3.4400	0.1812	0.7768	0.0803
23	410	0.0122	0.4757	0.3252	0.4270	0.7146	3.1538	0.1589	0.8947	0.0912
24	522	0.0118	0.3830	0.2886	0.2874	0.7976	3.5077	0.1465	0.7129	0.0831
25	472	0.0141	0.4538	0.2374	0.2915	0.7707	3.4822	0.1724	0.7065	0.0948
26	502	-	-	0.2764	-	-	-	-	0.6984	-
27	526	-	-	0.2253	-	-	-	-	0.6823	-
28	461	-	-	0.2744	-	-	-	-	0.6763	-
29	525	-	-	0.2529	-	-	-	-	0.5802	-
30	486	-	-	0.2864	-	-	-	-	0.8214	-

- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 (continued) Absolute Organ Weights with Corresponding Relative Organ Weights (% of Bodyweight) - Individual Values

Non-Recovery Females

DOSE LEVEL: 50 mg/kg/day

Animal Number	Bodyweight (g) at Terminal Kill	Organ Weight (g)							
		Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus
31	329	0.0727	1.8274	1.1259	2.0455	13.6077	0.1120	0.6102	0.2168
32	309	0.0848	1.9805	1.0762	2.1097	14.0765	0.1202	0.5738	0.2785
33	312	0.0548	1.9050	0.9852	1.8175	14.1829	0.1412	0.4919	0.1685
34	335	0.0932	1.9728	1.1376	2.2444	15.6958	0.1437	0.4418	0.3055
35	320	0.0766	1.8634	1.0871	2.0045	13.9127	0.1119	0.6027	0.3666
36	302	-	-	-	-	-	0.1257	-	-
37	273	-	-	-	-	-	■	-	-
38	324	-	-	-	-	-	0.1459	-	-
39	326	-	-	-	-	-	0.1571	-	-
40 NP	-	-	-	-	-	-	-	-	-

Animal Number	Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)							
		Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus
31	329	0.0221	0.5554	0.3422	0.6217	4.1361	0.0340	0.1855	0.0659
32	309	0.0274	0.6409	0.3483	0.6828	4.5555	0.0389	0.1857	0.0901
33	312	0.0176	0.6106	0.3158	0.5825	4.5458	0.0453	0.1577	0.0540
34	335	0.0278	0.5889	0.3396	0.6700	4.6853	0.0429	0.1319	0.0912
35	320	0.0239	0.5823	0.3397	0.6264	4.3477	0.0350	0.1883	0.1146
36	302	-	-	-	-	-	0.0416	-	-
37	273	-	-	-	-	-	■	-	-
38	324	-	-	-	-	-	0.0450	-	-
39	326	-	-	-	-	-	0.0482	-	-
40 NP	-	-	-	-	-	-	-	-	-

NP = not pregnant
■ = data unavailable
- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 (continued) Absolute Organ Weights with Corresponding Relative Organ Weights (% of Bodyweight) - Individual Values

Non-Recovery Males

DOSE LEVEL: 175 mg/kg/day

Animal Number	Bodyweight (g) at Terminal Kill	Organ Weight (g)								
		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Spleen	Testes	Thymus
41	509	0.0634	2.1552	1.3360	1.8490	4.9632	19.9741	0.8845	3.7955	0.4485
42	519	0.0524	1.8760	1.3236	1.5898	4.3624	21.4580	0.8528	3.6586	0.3628
43	446	0.0573	2.0317	1.1984	1.5195	3.2393	16.7796	0.5667	3.4034	0.3888
44	450	0.0611	2.0836	1.1523	1.3045	3.6697	17.2198	0.6385	3.4868	0.2601
45	441	0.0764	1.9986	1.4669	1.4435	3.6540	17.1469	0.8073	3.7631	0.4197
46	462	-	-	1.3342	-	-	-	-	3.5462	-
47	519	-	-	1.2611	-	-	-	-	3.7434	-
48	547	-	-	1.2798	-	-	-	-	4.1214	-
49	528	-	-	1.4079	-	-	-	-	3.4042	-
50	507	-	-	1.4663	-	-	-	-	3.6651	-

Animal Number	Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)								
		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Spleen	Testes	Thymus
41	509	0.0125	0.4234	0.2625	0.3633	0.9751	3.9242	0.1738	0.7457	0.0881
42	519	0.0101	0.3615	0.2550	0.3063	0.8405	4.1345	0.1643	0.7049	0.0699
43	446	0.0128	0.4555	0.2687	0.3407	0.7263	3.7622	0.1271	0.7631	0.0872
44	450	0.0136	0.4630	0.2561	0.2899	0.8155	3.8266	0.1419	0.7748	0.0578
45	441	0.0173	0.4532	0.3326	0.3273	0.8286	3.8882	0.1831	0.8533	0.0952
46	462	-	-	0.2888	-	-	-	-	0.7676	-
47	519	-	-	0.2430	-	-	-	-	0.7213	-
48	547	-	-	0.2340	-	-	-	-	0.7535	-
49	528	-	-	0.2666	-	-	-	-	0.6447	-
50	507	-	-	0.2892	-	-	-	-	0.7229	-

- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 (continued) Absolute Organ Weights with Corresponding Relative Organ Weights (% of Bodyweight) - Individual Values

Non-Recovery Females

DOSE LEVEL: 175 mg/kg/day

Animal Number	Bodyweight (g) at Terminal Kill	Organ Weight (g)							
		Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus
51	324	0.1014	2.0190	1.0592	2.6812	14.9878	0.1135	0.6230	0.3527
52	368	0.1004	1.9537	1.2056	2.3792	18.7077	0.1449	0.6240	0.4195
53	313	0.0759	1.8678	1.1179	2.3580	16.2443	0.1408	0.6538	0.3490
54	333	0.1038	1.9275	1.0118	2.5802	15.1633	0.1375	0.7270	0.4157
55	349	0.0915	1.9092	1.1362	2.5559	15.7469	0.1365	0.7603	0.4239
56	334	-	-	-	-	-	0.1180	-	-
57	318	-	-	-	-	-	0.1002	-	-
58	320	-	-	-	-	-	0.1378	-	-
59	299	-	-	-	-	-	0.1173	-	-
60	305	-	-	-	-	-	0.1214	-	-

Animal Number	Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)							
		Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus
51	324	0.0313	0.6231	0.3269	0.8275	4.6259	0.0350	0.1923	0.1089
52	368	0.0273	0.5309	0.3276	0.6465	5.0836	0.0394	0.1696	0.1140
53	313	0.0242	0.5967	0.3572	0.7534	5.1899	0.0450	0.2089	0.1115
54	333	0.0312	0.5788	0.3038	0.7748	4.5535	0.0413	0.2183	0.1248
55	349	0.0262	0.5470	0.3256	0.7323	4.5120	0.0391	0.2179	0.1215
56	334	-	-	-	-	-	0.0353	-	-
57	318	-	-	-	-	-	0.0315	-	-
58	320	-	-	-	-	-	0.0431	-	-
59	299	-	-	-	-	-	0.0392	-	-
60	305	-	-	-	-	-	0.0398	-	-

- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 (continued) Absolute Organ Weights with Corresponding Relative Organ Weights (% of Bodyweight) - Individual Values

Non-Recovery Males

DOSE LEVEL: 600 mg/kg/day

Animal Number	Bodyweight (g) at Terminal Kill	Organ Weight (g)								
		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Spleen	Testes	Thymus
61	482	0.0645	2.1864	1.3825	1.8229	3.9849	21.9745	0.7851	3.7706	0.3336
62	412	0.0445	2.0040	1.3948	1.7931	3.3314	16.8085	0.6751	3.3729	0.3929
63	344	0.0226■	1.9763	1.2283	1.1084	2.6924	13.5362	0.6180	3.0278	0.3074
64	410	0.0546	1.9633	0.9790	1.4470	3.3036	18.1207	0.6555	2.6394	0.3585
65	399	0.0612	1.9387	1.0978	1.3060	3.6424	18.0602	0.5037	3.1031	0.3288
66	471	-	-	1.3860	-	-	-	-	4.0043	-
67	440	-	-	1.1444	-	-	-	-	3.0549	-
68	422	-	-	1.1315	-	-	-	-	3.4359	-
69	420	-	-	1.4612	-	-	-	-	4.1292	-
70	402	-	-	1.1031	-	-	-	-	3.3360	-

Animal Number	Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)								
		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Spleen	Testes	Thymus
61	482	0.0134	0.4536	0.2868	0.3782	0.8267	4.5590	0.1629	0.7823	0.0692
62	412	0.0108	0.4864	0.3385	0.4352	0.8086	4.0797	0.1639	0.8187	0.0954
63	344	0.0066	0.5745	0.3571	0.3222	0.7827	3.9349	0.1797	0.8802	0.0894
64	410	0.0133	0.4789	0.2388	0.3529	0.8058	4.4197	0.1599	0.6438	0.0874
65	399	0.0153	0.4859	0.2751	0.3273	0.9129	4.5264	0.1262	0.7777	0.0824
66	471	-	-	0.2943	-	-	-	-	0.8502	-
67	440	-	-	0.2601	-	-	-	-	0.6943	-
68	422	-	-	0.2681	-	-	-	-	0.8142	-
69	420	-	-	0.3479	-	-	-	-	0.9831	-
70	402	-	-	0.2744	-	-	-	-	0.8299	-

■ = only 1 adrenal weighed; value excluded from mean and sd
- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 (continued) Absolute Organ Weights with Corresponding Relative Organ Weights (% of Bodyweight) - Individual Values

Non-Recovery Females

DOSE LEVEL: 600 mg/kg/day

Animal Number	Bodyweight (g) at Terminal Kill	Organ Weight (g)							
		Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus
71	288	0.0789	1.5859	0.8547	1.9771	15.9445	0.1018	0.4900	0.1844
72	287	0.0625	1.8758	1.0205	1.9663	15.3920	0.0893	0.3983	0.2863
73	298	0.0578	1.8427	0.9077	1.9551	13.9282	0.1567	0.4826	0.2289
74	311	0.0615	1.6352	0.9897	2.3265	17.8033	0.1165	0.4467	0.1958
75	300	0.0733	1.7874	1.1207	2.2481	17.0114	0.2528	0.4660	0.3238
76	299	-	-	-	-	-	0.1574	-	-
77	306	-	-	-	-	-	0.1102	-	-
78	303	-	-	-	-	-	0.1025	-	-
79	296	-	-	-	-	-	0.1120	-	-
80	291	-	-	-	-	-	0.1513	-	-

Animal Number	Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)							
		Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus
71	288	0.0274	0.5507	0.2968	0.6865	5.5363	0.0353	0.1701	0.0640
72	287	0.0218	0.6536	0.3556	0.6851	5.3631	0.0311	0.1388	0.0998
73	298	0.0194	0.6184	0.3046	0.6561	4.6739	0.0526	0.1619	0.0768
74	311	0.0198	0.5258	0.3182	0.7481	5.7245	0.0375	0.1436	0.0630
75	300	0.0244	0.5958	0.3736	0.7494	5.6705	0.0843	0.1553	0.1079
76	299	-	-	-	-	-	0.0526	-	-
77	306	-	-	-	-	-	0.0360	-	-
78	303	-	-	-	-	-	0.0338	-	-
79	296	-	-	-	-	-	0.0378	-	-
80	291	-	-	-	-	-	0.0520	-	-

- = not applicable

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 (continued) Absolute Organ Weights with Corresponding Relative Organ Weights (% of Bodyweight) - Individual Values

Recovery Males

DOSE LEVEL: 0 (control)

Animal Number	Bodyweight (g) at Terminal Kill	Organ Weight (g)								
		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Spleen	Testes	Thymus
81	496	0.0496	2.0783	1.3908	1.5981	3.6345	16.1961	0.8355	3.8223	0.3391
82	440	0.0651	1.9616	1.3955	1.7905	3.2387	14.5904	0.7449	3.6526	0.3133
83	512	0.0518	2.0688	1.3204	1.8889	3.7890	17.6410	0.8655	3.1326	0.3989
84	586	0.0724	2.4473	1.5569	1.9403	3.9345	18.9491	0.9774	3.9297	0.2783
85	607	0.0586	2.0922	1.5629	1.7356	4.1271	18.6005	0.9334	3.5359	0.5324

Animal Number	Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)								
		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Spleen	Testes	Thymus
81	496	0.0100	0.4190	0.2804	0.3222	0.7328	3.2653	0.1684	0.7706	0.0684
82	440	0.0148	0.4458	0.3172	0.4069	0.7361	3.3160	0.1693	0.8301	0.0712
83	512	0.0101	0.4041	0.2579	0.3689	0.7400	3.4455	0.1690	0.6118	0.0779
84	586	0.0124	0.4176	0.2657	0.3311	0.6714	3.2336	0.1668	0.6706	0.0475
85	607	0.0097	0.3447	0.2575	0.2859	0.6799	3.0643	0.1538	0.5825	0.0877

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 (continued) Absolute Organ Weights with Corresponding Relative Organ Weights (% of Bodyweight) - Individual Values

Recovery Females

DOSE LEVEL: 0 (Control)

Animal Number	Bodyweight (g) at Terminal Kill	Organ Weight (g)							
		Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus
86	263	0.0647	1.8293	0.9347	1.6575	8.5567	0.1391	0.5086	0.2180
87	300	0.0559	1.9064	1.2807	2.1690	11.6206	0.1037	0.6142	0.3359
88	264	0.0778	1.7813	0.9362	2.0578	9.5786	0.1282	0.6220	0.4502
89	298	0.0629	1.8954	1.2613	2.2160	10.0812	0.1147	0.5853	0.5144
90	303	0.0631	1.8043	0.9805	2.1841	10.8588	0.1725	0.6566	0.3911

Animal Number	Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)							
		Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus
86	263	0.0246	0.6956	0.3554	0.6302	3.2535	0.0529	0.1934	0.0829
87	300	0.0186	0.6355	0.4269	0.7230	3.8735	0.0346	0.2047	0.1120
88	264	0.0295	0.6747	0.3546	0.7795	3.6283	0.0486	0.2356	0.1705
89	298	0.0211	0.6360	0.4233	0.7436	3.3830	0.0385	0.1964	0.1726
90	303	0.0208	0.5955	0.3236	0.7208	3.5838	0.0569	0.2167	0.1291

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 (continued) Absolute Organ Weights with Corresponding Relative Organ Weights (% of Bodyweight) - Individual Values

Recovery Males

DOSE LEVEL: 600 mg/kg/day Recovery

Animal Number	Bodyweight (g) at Terminal Kill	Organ Weight (g)								
		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Spleen	Testes	Thymus
91	461	0.0672	2.1282	1.2735	1.5651	3.4248	16.4380	0.7818	3.4428	0.3581
92	493	0.0614	2.1060	1.4200	1.5264	4.3814	20.1583	0.7594	3.8891	0.3633
93	526	0.0665	2.0714	1.5696	1.8875	3.8794	20.3055	0.7491	3.9966	0.4098
94	429	0.0593	1.9373	1.3044	1.3413	3.4828	17.3667	0.6943	3.4466	0.3727
95	422	0.0688	1.9763	1.1522	1.6491	3.1786	14.8406	0.7357	3.4055	0.2912

Animal Number	Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)								
		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Spleen	Testes	Thymus
91	461	0.0146	0.4616	0.2762	0.3395	0.7429	3.5657	0.1696	0.7468	0.0777
92	493	0.0125	0.4272	0.2880	0.3096	0.8887	4.0889	0.1540	0.7889	0.0737
93	526	0.0126	0.3938	0.2984	0.3588	0.7375	3.8604	0.1424	0.7598	0.0779
94	429	0.0138	0.4516	0.3041	0.3127	0.8118	4.0482	0.1618	0.8034	0.0869
95	422	0.0163	0.4683	0.2730	0.3908	0.7532	3.5167	0.1743	0.8070	0.0690

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 19 (continued) Absolute Organ Weights with Corresponding Relative Organ Weights (% of Bodyweight) - Individual Values

Recovery Females

DOSE LEVEL: 600 mg/kg/day Recovery

Animal Number	Bodyweight (g) at Terminal Kill	Organ Weight (g)							
		Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus
96	288	0.0549	1.9186	1.2696	2.0322	10.0980	0.1212	0.5110	0.4008
97	259	0.0670	1.6965	0.9339	2.1432	11.1012	0.1602	0.5373	0.5029
98	286	0.0762	2.0661	1.8407	2.4629	12.4201	0.0975	0.6862	0.3718
99	270	0.0651	1.7278	1.0238	2.2001	11.7240	0.1420	0.6342	0.3895
100	257	0.0457	1.8589	1.2716	2.0311	9.9497	0.1285	0.4660	0.3386

Animal Number	Bodyweight (g) at Terminal Kill	Relative Organ Weight (%)							
		Adrenals	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus
96	288	0.0191	0.6662	0.4408	0.7056	3.5063	0.0421	0.1774	0.1392
97	259	0.0259	0.6550	0.3606	0.8275	4.2862	0.0619	0.2075	0.1942
98	286	0.0266	0.7224	0.6436	0.8612	4.3427	0.0341	0.2399	0.1300
99	270	0.0241	0.6399	0.3792	0.8149	4.3422	0.0526	0.2349	0.1443
100	257	0.0178	0.7233	0.4948	0.7903	3.8715	0.0500	0.1813	0.1318

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 Individual Histopathological Findings

DOSE LEVEL: 0 (Control)

Animal Number and Sex	Mode of Death	Tissue	Observation
1 M	Terminal kill	Adrenals	Cortical vacuolation (minimal)
		Bone marrow	Adipose infiltration (slight)
		Heart	Focal myocarditis (minimal)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Pituitary	Vacuolation pars anterior cells (slight)
		Spleen	Extramedullary haemopoiesis (minimal)
2 M	Terminal kill	Bone marrow	Adipose infiltration (moderate)
		Kidneys	Groups of basophilic tubules (minimal)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Pituitary	Vacuolation pars anterior cells (slight)
		Spleen	Extramedullary haemopoiesis (minimal)
		Thyroids	Follicular cell hypertrophy (minimal)
3 M	Terminal kill	Bone marrow	Adipose infiltration (moderate)
		Heart	Focal myocarditis (minimal)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Pancreas	Exocrine atrophy (slight)
		Pituitary	Vacuolation pars anterior cells (minimal)
		Spleen	Extramedullary haemopoiesis (minimal)
4 M	Terminal kill	Bone marrow	Adipose infiltration (slight)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Pituitary	Vacuolation pars anterior cells (minimal)
		Spleen	Extramedullary haemopoiesis (minimal)
5 M	Terminal kill	Aorta	No tissue available
		Bone marrow	Adipose infiltration (minimal)
		Heart	Focal myocarditis (minimal)
		Kidneys	Groups of basophilic tubules (minimal)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Pituitary	Vacuolation pars anterior cells (minimal)
		Spleen	Extramedullary haemopoiesis (minimal)
		Thyroids	Follicular cell hypertrophy (minimal)

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 0 (Control)

Animal Number and Sex	Mode of Death	Tissue	Observation
6 M	Terminal kill	Pituitary	Vacuolation pars anterior cells (minimal)
7 M	Terminal kill	Pituitary	Vacuolation pars anterior cells (minimal)
		Prostate	Epithelial and subepithelial inflammatory cells (minimal)
8 M	Terminal kill	Pituitary	Vacuolation pars anterior cells (minimal)
9 M	Terminal kill	Pituitary	Vacuolation pars anterior cells (minimal)
10 M	Terminal kill	Pituitary	Vacuolation pars anterior cells (minimal)

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 0 (Control)

Animal Number and Sex	Mode of Death	Tissue	Observation
11 F	Terminal kill	Bone marrow	Adipose infiltration (minimal)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Mammary gland	Glandular hyperplasia
		Spleen	Extramedullary haemopoiesis (minimal)
		Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
12 F	Terminal kill	Bone marrow	Adipose infiltration (slight)
		Heart	Focal myocarditis (minimal)
		Kidneys	Groups of basophilic tubules (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
			Groups of alveolar macrophages (minimal)
		Mammary gland	Glandular hyperplasia
		Pancreas	Exocrine atrophy (minimal)
		Skeletal muscle	Mononuclear cell foci (minimal)
		Spleen	Extramedullary haemopoiesis (minimal)
		Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
13 F	Terminal kill	Bone marrow	Adipose infiltration (minimal)
		Liver	Generalised hepatocyte enlargement (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
			Groups of alveolar macrophages (minimal)
		Mammary gland	Glandular hyperplasia
		Spleen	Extramedullary haemopoiesis (slight)
		Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
14 F	Terminal kill	Bone marrow	Adipose infiltration (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Mammary gland	Glandular hyperplasia
		Spleen	Extramedullary haemopoiesis (minimal)

F = female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 0 (Control)

Animal Number and Sex	Mode of Death	Tissue	Observation
15 F	Interim Death	Bone marrow	Adipose infiltration (minimal)
		Caecum	Submucosal oedema
		Heart	Focal myocarditis (minimal)
		Liver	Hepatocyte basophilia
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Mammary gland	Glandular hyperplasia
		Spleen	Extramedullary haemopoiesis (minimal)
		Thymus	Atrophy (severe)
		Urinary bladder	Peripheral oedema
		Uterus/Cervix	Dilatation horn1 (moderate)
			Dilatation horn2 (moderate)
			Peripheral oedema and inflammatory cells
16 F	Terminal kill	Bone marrow	Adipose infiltration (slight)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
			Focal pneumonitis (minimal)
		Mammary gland	Glandular hyperplasia
		Spleen	Extramedullary haemopoiesis (minimal)
		Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
17 F	Terminal kill	Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
18 F	Terminal kill	Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
19 F	Terminal kill	Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
20 F	Terminal kill	Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment

F = female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 50 mg/kg/day

Animal Number and Sex	Mode of Death	Tissue	Observation
21 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Thyroids	Follicular cell hypertrophy (minimal)
22 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Thyroids	Follicular cell hypertrophy (minimal)
23 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Oesophagus	Inflammatory cells peripheral musculature
		Thyroids	Follicular cell hypertrophy (minimal)
24 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Oesophagus	Inflammatory cells peripheral musculature
		Thyroids	Follicular cell hypertrophy (minimal)
25 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Thyroids	Follicular cell hypertrophy (slight)

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 50 mg/kg/day

Animal Number and Sex	Mode of Death	Tissue	Observation
31 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
32 F	Terminal kill	Liver	Mononuclear cell foci (minimal) Generalised hepatocyte enlargement (minimal)
33 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
34 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
35 F	Terminal kill	Liver Thyroids	Mononuclear cell foci (minimal) Focal hepatocyte necrosis (minimal) Follicular cell hypertrophy (minimal)

F = female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 175 mg/kg/day

Animal Number and Sex	Mode of Death	Tissue	Observation
41 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Thyroids	Follicular cell hypertrophy (minimal)
42 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Thyroids	Follicular cell hypertrophy (minimal)
43 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
44 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
45 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Oesophagus	Inflammatory cells peripheral musculature
		Thyroids	Follicular cell hypertrophy (minimal)

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 175 mg/kg/day

Animal Number and Sex	Mode of Death	Tissue	Observation
51 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Oesophagus	Inflammatory cells peripheral musculature
		Thyroids	Follicular cell hypertrophy (minimal)
52 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Oesophagus	Inflammatory cells peripheral musculature
53 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
			Generalised hepatocyte enlargement (minimal)
		Oesophagus	Inflammatory cells peripheral musculature
54 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
			Generalised hepatocyte enlargement (slight)
		Oesophagus	Inflammatory cells peripheral musculature
		Thyroids	Follicular cell hypertrophy (minimal)
55 F	Terminal kill	Liver	Mononuclear cell foci (minimal)

F = female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 600 mg/kg/day

Animal Number and Sex	Mode of Death	Tissue	Observation
61 M	Terminal kill	Bone marrow	Adipose infiltration (minimal)
		Kidneys	Groups of basophilic tubules (minimal)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Mesenteric lymph node	Vacuolation histiocytes (moderate)
		Oesophagus	Inflammatory cells peripheral musculature
		Pituitary	Vacuolation pars anterior cells (minimal)
		Spleen	Extramedullary haemopoiesis (minimal)
62 M	Terminal kill	Bone marrow	Adipose infiltration (slight)
		Coagulating glands	one section examined
		Kidneys	Groups of basophilic tubules (minimal)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Mammary gland	No tissue available
		Pituitary	Vacuolation pars anterior cells (minimal)
		Spleen	Extramedullary haemopoiesis (minimal)
63 M	Terminal kill	Adrenals	one section examined
		Bone marrow	Adipose infiltration (slight)
		Kidneys	Globular accumulations of eosinophilic material (minimal)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Pituitary	Vacuolation pars anterior cells (minimal)
		Spleen	Extramedullary haemopoiesis (minimal)
64 M	Terminal kill	Adrenals	Cortical vacuolation (minimal)
		Bone marrow	Adipose infiltration (moderate)
		Heart	Focal myocarditis (minimal)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
			Groups of alveolar macrophages (minimal)
		Pituitary	Vacuolation pars anterior cells (slight)
		Prostate	Epithelial and subepithelial inflammatory cells (minimal)
		Spleen	Extramedullary haemopoiesis (minimal)
		Testes	Atrophy gonad 1 (minimal)

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 600 mg/kg/day

Animal Number and Sex	Mode of Death	Tissue	Observation
65 M	Terminal kill	Bone marrow	Adipose infiltration (slight)
		Kidneys	Groups of basophilic tubules (slight)
			Globular accumulations of eosinophilic material (minimal)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Pituitary	Vacuolation pars anterior cells (minimal)
		Spleen	Extramedullary haemopoiesis (minimal)
		Thyroids	Follicular cell hypertrophy (minimal)
66 M	Terminal kill	Pituitary	Vacuolation pars anterior cells (minimal)
		Prostate	Epithelial and subepithelial inflammatory cells (slight)
67 M	Terminal kill	Pituitary	Vacuolation pars anterior cells (minimal)
68 M	Terminal kill	Pituitary	Vacuolation pars anterior cells (minimal)
		Prostate	Epithelial and subepithelial inflammatory cells (slight)
69 M	Terminal kill	Coagulating glands	one section examined
		Pituitary	Vacuolation pars anterior cells (minimal)
70 M	Terminal kill	Pituitary	Vacuolation pars anterior cells (slight)

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 600 mg/kg/day

Animal Number and Sex	Mode of Death	Tissue	Observation
71 F	Terminal kill	Bone marrow	Adipose infiltration (slight)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Mammary gland	Glandular hyperplasia
		Oesophagus	Inflammatory cells peripheral musculature
		Spleen	Extramedullary haemopoiesis (minimal)
		Thyroids	Follicular cell hypertrophy (minimal)
		Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
72 F	Terminal kill	Bone marrow	Adipose infiltration (minimal)
		Liver	Mononuclear cell foci (minimal)
			Centrilobular hepatocyte enlargement (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
			Groups of alveolar macrophages (minimal)
		Mammary gland	Glandular hyperplasia
		Oesophagus	Inflammatory cells peripheral musculature
		Spleen	Extramedullary haemopoiesis (minimal)
		Thyroids	Follicular cell hypertrophy (minimal)
		Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
73 F	Terminal kill	Bone marrow	Adipose infiltration (slight)
		Kidneys	Groups of basophilic tubules (minimal)
		Liver	Centrilobular hepatocyte enlargement (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Mammary gland	Glandular hyperplasia
		Oesophagus	Inflammatory cells peripheral musculature
		Spinal cord	No tissue available
		Spleen	Extramedullary haemopoiesis (minimal)
		Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment

F = female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 600 mg/kg/day

Animal Number and Sex	Mode of Death	Tissue	Observation
74 F	Terminal kill	Bone marrow	Adipose infiltration (minimal)
		Duodenum	Mucosal hypertrophy
		Liver	Mononuclear cell foci (minimal)
			Centrilobular hepatocyte enlargement (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
			Groups of alveolar macrophages (minimal)
		Mammary gland	Glandular hyperplasia
		Oesophagus	Inflammatory cells peripheral musculature
		Spleen	Extramedullary haemopoiesis (minimal)
		Thyroids	Follicular cell hypertrophy (minimal)
		Uterus/cervix	Peripheral foam cells/haemorrhage/pigment
75 F	Terminal kill	Bone marrow	Adipose infiltration (moderate)
		Kidneys	Groups of basophilic tubules (minimal)
		Liver	Mononuclear cell foci (minimal)
		Lungs	Perivascular/peribronchiolar lymphoid aggregations (minimal)
		Mammary gland	Glandular hyperplasia
		Spleen	Extramedullary haemopoiesis (minimal)
		Thyroids	Follicular cell hypertrophy (slight)
		Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
76 F	Terminal kill	Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
77 F	Terminal kill	Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
78 F	Terminal kill	Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
		Vagina	No tissue available
79 F	Terminal kill	Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment
80 F	Terminal kill	Uterus/Cervix	Peripheral foam cells/haemorrhage/pigment

F = female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 0 (Control) Recovery

Animal Number and Sex	Mode of Death	Tissue	Observation
81 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
82 M	Terminal kill	Liver Oesophagus	Mononuclear cell foci (minimal) Inflammatory cells peripheral musculature
83 M	Terminal kill	Liver Thyroids	Mononuclear cell foci (minimal) Follicular cell hypertrophy (minimal)
84 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
85 M	Terminal kill	Liver	Mononuclear cell foci (minimal)

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 0 (Control) Recovery

Animal Number and Sex	Mode of Death	Tissue	Observation
86 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
87 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
88 F	Terminal kill		No abnormality detected
89 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
90 F	Terminal kill	Liver	Mononuclear cell foci (minimal)

F = female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 600 mg/kg/day Recovery

Animal Number and Sex	Mode of Death	Tissue	Observation
91 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Oesophagus	Inflammatory cells peripheral musculature
92 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Thyroids	Follicular cell hypertrophy (minimal)
93 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
			Centrilobular hepatocyte enlargement (minimal)
94 M	Terminal kill	Thyroids	Follicular cell hypertrophy (minimal)
95 M	Terminal kill	Liver	Mononuclear cell foci (minimal)
		Thyroids	Follicular cell hypertrophy (minimal)

M = male

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 20 (continued) Individual Histopathological Findings

DOSE LEVEL: 600 mg/kg/day Recovery

Animal Number and Sex	Mode of Death	Tissue	Observation
96 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
97 F	Terminal kill	Oesophagus Thyroids	Inflammatory cells peripheral musculature Follicular cell hypertrophy (minimal)
98 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
99 F	Terminal kill	Liver	Mononuclear cell foci (minimal)
100 F	Terminal kill	Liver	Mononuclear cell foci (minimal)

F = female

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 21 Protocol

SafePharm Laboratories

PROTOCOL

TEST MATERIAL	:	1,5-Cyclooctadiene (COD), 3- Pentenitrile (3PN), Triisopropylborate (TIPB), Triphenylboron (TPB)
STUDY TYPE	:	Oral (Gavage) Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in the Rat (OECD 422 1996 With Recovery Groups)
PROJECT NUMBER	:	2231/0007
PROPOSED START DATE	:	August 2006
PROPOSED COMPLETION DATE	:	September 2006
TARGET (DRAFT) REPORT DATE	:	January 2007
SPONSOR	:	INVISTA S.a.r.l. INVISTA Building 4123 East 37th Street North Wichita KS 67201 UNITED STATES OF AMERICA

APPROVED FOR SPONSOR BY: ..... DATE: 12/06/06

AUTHORISED BY: ..... DATE: 20 June 2006

J DUNSTER BSc (Hons)
STUDY DIRECTOR

This protocol is issued without signature by the Study Director to enable changes to be made if necessary prior to authorisation. Sponsors should sign and return the document to indicate approval and GLP authorisation will be confirmed by the Study Director's signature prior to the start of the study.

Appendix 21 (continued) Protocol

ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

1. INTRODUCTION AND OBJECTIVES

This protocol details a study designed to comply with the recommendations of the OECD Guidelines for Testing of Chemicals No 422 "Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test" (adopted 22.03.96).

The purpose of this study is to establish the effects of repeated oral administration of the test material to rats over a period of up to fifty-four days. The results of the study are believed to be of value in predicting the toxicity of the test material to man and can identify the organs and tissues which may be injured by exposure, can enable detection of possible cumulative toxicity and the estimation of the "No Observed Effect Level" (NOEL). The study is also designed to screen for potential adverse effects on reproduction.

The work will be performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106)). These regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 2004/9/EC and 2004/10/EC.

These international standards are acceptable to the Regulatory agencies of the following countries: Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Israel, Italy, Japan, Republic of Korea, Luxembourg, Mexico, The Netherlands, New Zealand, Norway, Poland, Portugal, Slovenia, South Africa, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the United States of America.

2. TEST FACILITY

Test Facility	**Test Site (histology processing)**
Safepharm Laboratories Ltd	Propath UK Ltd
Shardlow Business Park	Willow Court
Shardlow	Netherwood Road
Derbyshire	Rotherwas
DE72 2GD	Hereford
	HR2 6JU

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 21 (continued) Protocol

3. ANIMALS

Specification

Sprague Dawley Crl:CD® (SD) IGS BR strain rats obtained from Charles River (UK) Limited, Margate, Kent. At the start of the study animals will be aged eight weeks. The weight variation will not exceed ±20% of the mean weight for either sex.

Justification

Preferred species of choice as historically used for safety evaluation studies and specified by appropriate regulatory authorities.

4. ANIMAL HUSBANDRY

Environment

Target temperature:	21 ± 2°C
Target humidity:	55 ± 15%
Lighting:	Twelve hours of continuous artificial light in each twenty-four hour period
Ventilation:	At least fifteen air changes per hour

Housing

Males and females during the pre-mating phases will be housed in groups of five by sex in polypropylene cages with stainless steel mesh lids and grid bases, suspended over trays containing absorbent paper. During mating one male and one female will be housed in similar caging. Males, following mating, will be re-housed in their original holding cages. Mated females, will be housed individually in solid floor polypropylene cages with stainless steel mesh lids and softwood flake bedding (Datesand Ltd, Cheshire, UK) for gestation, birth and lactation periods.

Diet and Water

Rodent PMI 5002 (Certified) diet (BCM IPS Ltd, London, UK) with batch analysis, and tap water *ad libitum*.

The diet and drinking water are routinely analysed and are considered not to contain any contaminant that could reasonably be expected to affect the purpose or integrity of the study.

5. ANIMAL WELFARE

Environmental Enrichment

Animals will be provided with environmental enrichment items: wooden chew blocks (B & K Universal Ltd, Hull, UK) and cardboard fun tunnels (Datesand Ltd, Cheshire, UK) or suitable alternatives. These enrichment items are routinely analysed and are considered not to contain any contaminant that could reasonably be expected to affect the purpose or integrity of the study.

Study Conduct

The study was designed and will be conducted to cause the minimum suffering or distress to the animals consistent with the scientific objectives and in accordance with the Safepharm policy on animal welfare. This standard test method is subject to review and the conduct of the study may be retrospectively reviewed, as part of the Safepharm Ethical Review Process.

6. PRE-TEST PROCEDURES

Acclimatisation Period

At least seven days.

Allocation

Animals will be allocated to dose groups using a randomisation procedure based on bodyweight.

Identification

Each animal, selected at random, will be uniquely identified within the study by ear-punch. A colour-coded cage card will be prepared with details of test material, project number, dose level, sex, numbers of animals, route of administration and Study Director responsible for the study.

7. TEST MATERIAL AND EXPERIMENTAL PREPARATION

Identification

Supplied by the Sponsor with details of purity, stability and hazardous properties if known. The integrity of supplied data, relating to the test material will be the responsibility of the Sponsor.

Storage

Room temperature unless otherwise specified by Sponsor.

Preparation

The test material will be dissolved or suspended in a suitable vehicle weekly (subject to confirmation of stability). Wherever possible, an aqueous formulation will be used, followed by consideration of formulation in vegetable oil (eg Arachis oil), then other specified vehicles. The method of preparation will be documented in the study records.

Analysis

Details of identification of the test material will be supplied by the Sponsor. The test material formulations will be analysed for concentration, stability and, if applicable, homogeneity by Safepharm Analytical Laboratory.

8. STUDY DESIGN

Administration

Once daily, by gavage, using a suitable dosing cannula attached to a graduated syringe for up to fifty-four days. Dosing will be performed at a similar time each day wherever possible.

Dose Groups

Six dose groups will be used. Groups will be allocated as follows:

Group Number	Group Designation	Number of animals	
		Male	Female
1	Control	10	10
2	Low	10	10
3	Intermediate	10	10
4	High	10	10
5	Recovery Control	5	5
6	Recovery High	5	5

Dose levels will be based on available toxicity data following a preliminary range-finder (Appendix 1), up to a maximum dose of 1000 mg/kg/day. The dose levels to be used in the study will be documented as a

protocol addendum together with the treatment volume. The control group will handled in an identical manner to the test animals, except for administration of the test material. The recovery groups will be used for evaluation of reversibility of toxic findings but will not be used for evaluation of reproductive effects.

Chronological Sequence of Study

Dose Groups 1 to 4 (non-recovery)

i) Groups of ten male and ten female rats will be dosed according to dose group for fourteen days prior to pairing.

ii) All animals will be given a detailed clinical examination once every week for four weeks to observe functional/behavioural changes in an open arena.

iii) One day prior to pairing (Day 13) five males and five females, randomly selected from each dose group, will be sampled for blood chemistry and haematology.

iv) On Day 14 animals will be paired on a one male:one female basis within each dose group for a maximum of fourteen days.

v) At the end of the mating period males will be returned to their original holding cages and females will be transferred to individual cages. Dosing will continue for both sexes during subsequent female gestation and lactation phases.

vi) At the end of the mating phase five males randomly selected from each dose group will be evaluated for functional/behaviourial changes together with sensory reactivity, grip strength and motor activity assessment.

vii) Pregnant females are allowed to give birth and maintain their offspring until Day 4 *post partum*. Evaluation of each litter will be performed during this period.

viii) At Day 4 *post partum*, five females per dose group will be selected for functional/behaviourial changes together with sensory reactivity, grip strength and motor activity assessment.

ix) At Day 5 *post partum* following completion of functional assessments all females and offspring will be killed and examined macroscopically.

x) Urinalysis will be performed on five randomly selected males from each dose group during the final week of dosing.

xi) Subject to confirmation of successful mating, males will be killed and examined macroscopically.

xii) Dependant upon previous results, additional blood sampling and behavioural investigations may be performed on males and/or females immediately prior to termination.

Dose Groups 5 and 6 (recovery)

i) Groups of five male and five female rats will be dosed according to dose group continuously up to the point of sacrifice of non-recovery males at which time treatment will be discontinued.

ii) The males and females will be maintained without treatment for fourteen days.

iii) Urinalysis will be performed for all males during the final week of recovery.

iv) After fourteen days of recovery males and females will be killed and examined macroscopically.

9. OBSERVATIONS

Morbidity/Mortality Inspection

Twice daily, early and late during the working period.

Clinical Observations

Individual clinical observations will be performed immediately before dosing and one hour after dosing. An additional observation will be made five hours after dosing during the normal working week (not at weekends or on public holidays). Recovery groups will be observed twice daily during the treatment-free period (once daily at weekends and on public holdays). All observations will be recorded.

Functional Observations

Detailed clinical observations will be performed on all non-recovery test and control group animals before the first exposure to the test material and once weekly thereafter up to Week 4. These observations will be performed outside the home cage, in a standard arena, at approximately two hours after dosing (where applicable) to ensure that any transient effects of treatment are identified. All observations will be recorded. In addition, sensory reactivity to different stimuli (eg auditory, visual and proprioceptive), grip

strength (fore and hind limb) and motor activity (using a 44 photobeam unit) will be measured, in five randomly selected non-recovery males per group, once during Week 4, at least two hours after dosing. Non-recovery females will be similarly evaluated at Day 4 *post partum*.

Bodyweights

Individual bodyweights will be recorded on Day 0 (the day before the start of dosing) and at weekly intervals thereafter. Mated females will be weighed on Day 0, 7, 14, and 20 of gestation and Day 1 and Day 4 of lactation. Individual bodyweights will also be recorded at terminal kill.

Food Consumption

Dietary intake will be recorded weekly prior to mating for each cage group. Weekly food efficiency (bodyweight gain/food intake) will be calculated. Dietary intake for mated females will be recorded on Day 0, 7, 14 and 20 of gestation and Day 1 and 4 of lactation.

Water Consumption

Monitored daily by visual inspection of water bottles. Measurement will be initiated if a treatment-related effect is suspected, at the discretion of the Study Director.

Laboratory Investigations

Haematological and blood chemical investigations will be performed on five males and five females, randomly selected from each non-recovery dose group on Day 13 and on all recovery group animals at the end of the fourteen day treatment-free period. Blood samples will be withdrawn from the lateral tail vein.

Further investigations may also be performed later in the study at the discretion of the Study Director.

Urinalytical investigations will be performed on five males randomly selected from each non-recovery dose group during the final week of dosing and on all recovery group males during the final week of the fourteen day treatment-free period. Urine samples will be collected by housing the animals overnight in metabolism cages under normal hydration but without access to food.

Haematology

Haemoglobin	Differential leucocyte count
Haematocrit	Erythrocyte indices
Erythrocyte count	: mean cell haemoglobin
Total leucocyte count	: mean cell volume

: mean cell haemoglobin concentration
Prothrombin time
Activated partial thromboplastin time
Platelet count
Reticulocyte count*

* Blood film will be prepared but only examined at Study Director's discretion

Blood Chemistry

Blood urea
Total protein
Albumin
Albumin/Globulin ratio (by calculation)
Sodium
Potassium
Chloride
Calcium
Inorganic phosphorus
Creatinine
Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Glucose
Total cholesterol
Total bilirubin

Urinalysis

Volume
Specific gravity
pH
Protein
Glucose
Ketones
Bilirubin
Urobilinogen
Reducing substances
Blood

Mating

One male and one female within each non-recovery dose group will be paired for up to fourteen days. The stage of the oestrous cycle will be recorded during this period for the females.

Mating will be confirmed by the presence of sperm in a vaginal smear. The day on which sperm are observed will be taken as Day 0 of gestation. Smearing of individual females will be discontinued when sperm are found. Mated females will be removed from the mating cage and housed individually. Mated males will be returned to their original holding cages.

Appendix 21 (continued) Protocol

Pregnancy and Parturition

For each pregnant female the following will be recorded:

i) Date of mating

ii) Date of parturition

iii) Duration of gestation

Litter Data

For each litter the following will be recorded:

i) Number of pups born

ii) Number and sex of pups alive recorded daily and reported on Day 1 and 4 *post partum*

iii) Clinical condition of pups from birth to Day 4 *post partum*

iv) Individual litter pup weights on Day 1 and 4 *post partum*

Post Mortem Studies

Post mortem studies will be performed on animals found dead or killed *in extremis* during the study and on all adult animals killed by intravenous overdose of sodium pentobarbitone followed by exsanguination at termination. Offspring will be killed by intracardiac overdose of sodium pentobarbitone.

Gross Examination

Full external and internal examination of all animals including offspring.

The corpora lutea of all ovaries from *post partum* females will be counted at necropsy.

The uterine implantation sites will be counted. The procedure may be enhanced using the technique proposed by Salewski [1]. Additionally the uteri of apparently non-pregnant females will be examined.

Organ Weights

Adrenals	Kidneys
Brain	Liver
Epididymides	Spleen
Heart	Testes

Appendix 21 (continued) Protocol

Thymus Ovaries

Carried out on all surviving animals at termination where appropriate.

Histopathology

Samples of the following tissues will be preserved from all animals in buffered 10% formalin except where stated:

Adrenals	Muscle (skeletal)
Aorta (thoracic)	Oesophagus
Bone & bone marrow (femur including stifle joint)	**Ovaries**
	Pancreas
Bone & bone marrow (sternum)	**Pituitary**
Brain (including cerebrum, cerebellum and pons)	**Prostate**
Caecum	Rectum
Coagulating gland	Salivary glands (submaxillary)
Colon	Sciatic nerve
Duodenum	**Seminal vesicles**
Epididymides*	Skin (hind/limb)
Eyes	Spinal cord (cervical)
Gross lesions	Spleen
Heart	Stomach
Ileum	**Testes ***
Jejunum	Thymus
Kidneys	Thyroid/parathyroid
Liver	Trachea
Lungs (with bronchi)#	Urinary bladder
Lymph nodes (cervical and mesenteric)	**Uterus/Cervix**
Mammary tissue	**Vagina**

* preserved in bouins fluid
# inflated to approximately normal inspiratory volume with buffered 10% formalin before immersion in fixative

Initially all tissues from:

a) all animals that die or are killed *in extremis* during the study

b) five males and five females, randomly selected from the non-recovery control and high dose groups

will be despatched to the Test Site (histology processing), routinely processed to paraffin wax, sectioned and stained with haematoxylin and eosin.

In addition the tissues shown in **bold** from all remaining non-recovery control and high dose animals will also be despatched and processed. Prepared slides will be sent to the Study Pathologist for histopathological examination whereupon special staining techniques may be used, where appropriate.

Where treatment-related lesions are seen in the high dose group, histopathological examination of the affected tissue(s) will be extended to five animals of each sex, randomly selected, from each of the remaining dose groups including recovery groups.

10. EVALUATION OF DATA

All data will be summarised in tabular form and analysed statistically, where appropriate, to assess the significance of intergroup differences.

Repeat Dose Toxicity Data

Haematological, blood chemical, organ weight (absolute and relative to terminal bodyweight), weekly bodyweight gain, quantitative functional performance, sensory reactivity and urinalytical data will be assessed for non-recovery groups, where appropriate, by linear regression analysis (for dose response relationships) followed by one way analysis of variance (ANOVA) incorporating a test for homogeneity of variance. Where variances are shown to be homogenous, pairwise comparisons will be conducted using Dunnetts's test. In the case of recovery group data, the analysis performed will be a two-tailed t-test incorporating Levene's test for homogeneity of variance. Where Levene's test shows unequal variances among either non-recovery or recovery group data, the affected parameters will be analysed using non-parametric methods: Krukal-Wallis ANOVA and Mann-Whitney "U" test.

Reproductive Indices

Where appropriate, data will be analysed statistically using Levene's test for homogeneity of variance followed by one way analysis of variance and pairwise comparison using a choice of versions of multiple comparison test; or Kruskal-Wallis non parametric one way analysis of variance and Mann Whitney "U" test/Wilcoxon signed rank test.

Reproductive and viability indices by Fisher's exact test or chi-squared probability test may be used, where applicable (Appendix 2).

11. QUALITY ASSURANCE

This protocol will be reviewed for GLP compliance and the final report will be audited by Safepharm Quality Assurance Unit. Study phases will be inspected as determined by Safepharm Quality Assurance Unit.

The histology phase will be audited in accordance with Test Site QA Standard Operating Procedures.

12. PROTOCOL AMENDMENTS

Amendments to this protocol will be made only by completion of an Amendment to Protocol form authorised by the Study Director.

13. REPORT

The Sponsor will be informed immediately of all relevant findings. A full report containing a description of the test material, detailed description of the experimental procedures, summary of the observations together with tabulated group mean and individual animal data, discussion and interpretation of the results will be presented. A draft report will be sent to the Sponsor for review and comments before issue of the final report.

14. ARCHIVE

Unless instructed otherwise by the Sponsor, specimens, all original data including histology phase data, and the final report will be retained in the Safepharm archives for five years, after which instructions will be sought as to further retention or disposal. Further retention or return of the data will be chargeable to the Sponsor.

Appendix 21 (continued) Protocol

15. REFERENCE

Salewski E (1964) Färbemethode zum makroskopischen Nachweis von Implantationsstellen am Uterus der Ratte. Naunyn - Schmiedebergs Arch Exp Path Pharmacol 247 367.

Appendix 21 (continued) Protocol

Appendix 1 Preliminary Fourteen-Day Repeated Dose Oral Range-Finder in the Rat

INTRODUCTION

The purpose of this range-finder is to provide information as the basis for selection of dose levels for an oral combined repeat dose toxicity study with reproduction/development toxicity screening test in the rat. It is a preliminary investigation forming part of the overall study and is not regarded as separate from the combined repeat dose study.

Animals will be observed with attention to clinical observations, bodyweight and gross pathology, for any adverse effects resulting from toxicity of the test material.

16. STUDY FACILITIES

As described for the combined repeat dose study, except that histopathology may not be required.

17. ANIMALS

As described for the combined repeat dose study.

18. ANIMAL HUSBANDRY

Environment

As described for the combined repeat dose study.

Housing

Groups of three by sex in polypropylene cages with stainless steel mesh lids and grid bases, suspended over trays containing absorbent paper.

Diet and Water

As described for the combined repeat dose study.

Appendix 21 (continued) Protocol

19. ANIMAL WELFARE

Environmental Enrichment

As described for the combined repeat dose study.

Study Conduct

As described for the combined repeat dose study.

20. PRE-TEST PROCEDURES

As described for the combined repeat dose study, except that animals will not be allocated to dose groups using total randomisation procedure.

21. TEST MATERIAL AND EXPERIMENTAL PREPARATION

Identification

As described for the combined repeat dose study.

Storage

As described for the combined repeat dose study.

Preparation

The test material will be dissolved or suspended in a suitable vehicle. Wherever possible an aqueous formulation will be used, followed by consideration of formulation in vegetable oil (eg Arachis oil), then other specified vehicles. Fresh formulations will be prepared each day and dosed within three hours of preparation. The method of preparation will be documented in the study records together with the treatment volume.

Analysis

Details of identification of the test material will be supplied by the Sponsor. No analysis of the formulations will be performed during the study but preliminary analytical work may be carried out to prepare for the combined repeat dose study.

Appendix 21 (continued) Protocol

22. STUDY DESIGN

Administration

Once daily, by gavage using a suitable dosing cannula attached to a graduated syringe, for up to fourteen consecutive days. Dosing will be performed at a similar time each day whenever possible.

Dose Groups

A number of dose groups will be used sufficient for the purpose of the study, each comprising six animals (three male and three female). Dose levels will be selected on the basis of available toxicity data. Where no data are available, preliminary sighting work may be performed to assist dose level selection, using one male and one female per dose level. This will be documented in the range-finder records.

Dose levels may be adjusted during the course of the range-finder so that distinct evidence of toxicity is observed in at least one dose level, up to a maximum dose of 1000 mg/kg/day. Control animals will be treated with vehicle alone.

23. OBSERVATIONS

Morbidity/Mortality Inspection

Twice daily, early and late during the working period.

Clinical Observations

Individual clinical observations will be performed immediately before dosing and one hour after dosing. All observations will be recorded.

Bodyweights

Individual bodyweights will be recorded on Day 1 (the first day of dosing) and at twice weekly intervals thereafter.

Post Mortem Studies

Carried out on animals dying or killed *in extremis* during the range-finder and on all animals killed by cervical dislocation at termination.

Appendix 21 (continued) Protocol

Gross Examination

Full external and internal examination of all animals.

Histopathology

At the discretion of the Study Director, samples of tissues showing macroscopic abnormalities will be preserved in buffered 10% formalin for possible future histopathological examination.

24. EVALUATION OF DATA

All data will be summarised in tabular form and used to provide the basis for the selection of dose levels for the combined repeat dose study.

25. QUALITY ASSURANCE

As described for the combined repeat dose study, except that histology may not be performed.

26. PROTOCOL AMENDMENTS

As described for the combined repeat dose study.

27. REPORT

Soon after completion of the study a brief summary of the results together with the recommended dose levels for use in the combined repeat dose study will be sent to the Sponsor. A detailed report containing a summary of the observations together with tabulated group mean and individual animal data will be included in the report. Separate reports for range-finding studies will not normally be issued.

28. ARCHIVE

As described for the combined repeat dose study, except that histology data may not be generated.

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 21 (continued) Protocol

Appendix 2 Reproductive Indices

$$\text{Mating Index} = \frac{\text{Number of animals mated}}{\text{Number of animals paired}} \times 100$$

$$\text{Pregnancy Index} = \frac{\text{Number of pregnant females}}{\text{Number of animals mated}} \times 100$$

$$\text{Parturition Index} = \frac{\text{Number of females delivering live pups}}{\text{Number of pregnant females}} \times 100$$

$$\text{Live Birth Index} = \frac{\text{Number of pups alive on Day 1}}{\text{Number of pups born}} \times 100$$

$$\text{Viability Index} = \frac{\text{Number of pups alive on Day 4}}{\text{Number of pups alive on Day 1}} \times 100$$

$$\text{Pre - implantation Loss} = \frac{\text{Number of corpora lutea - number of implantations}}{\text{Number of corpora lutea}} \times 100$$

$$\text{Post - implantation Loss} = \frac{\text{Number of implantation - number of live foetuses}}{\text{Number of implantations}} \times 100$$

% Male pups (Sex Ratio) at birth will be calculated as:

$$\frac{\text{Number of male pups}}{\text{Number of pups of determined sex}} \times 100$$

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 21 (continued) Protocol

RESPONSIBLE PERSONNEL

PROJECT NUMBER: 2231/0007	**ISSUE NUMBER: 1**

HOME OFFICE PROJECT LICENCE NUMBER: PPL 40/2432/19B2

TITLE	NAME	REPLACEMENT DATE
STUDY DIRECTOR	J DUNSTER	
REPLACEMENT STUDY DIRECTOR	N K DHINSA	
STUDY PATHOLOGIST	P N BROOKS	
PROJECT LICENCE HOLDER	E WOOD	
OPERATIONS SUPERVISOR	N SZYSLER	
ANIMAL HUSBANDRY	N SZYSLER	
ANIMAL HEALTH	M TRUSSELL	
CLINICAL PATHOLOGY	J KEMP	
HISTOLOGY		
: LABORATORY	PROPATH UK LTD	
: PRINCIPAL INVESTIGATOR	T HILLING	
FORMULATION	R WOODARD	
CHEMICAL ANALYSIS	J McKENZIE	
DATA PROCESSING	D CLULOW	

QUALITY ASSURANCE		
TEST FACILITY	SAFEPHARM LABORATORIES LTD	
TEST SITE	PROPATH UK LTD	

PROPOSED DATES			
ANIMALS ON SITE	08 AUGUST 2006	STUDY TERMINATION	27 SEPTEMBER 2006
FIRST TREATMENT	16 AUGUST 2006	DRAFT REPORT	JANUARY 2007

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 21 (continued) Protocol

SAFEPHARM LABORATORIES LIMITED

PROTOCOL ADDENDUM

ADDENDUM NUMBER: One

PROTOCOL TITLE: Oral (Gavage) Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in the Rat (OECD 422 1996 With Recovery Groups)

TEST MATERIAL: 1,5-Cyclooctadiene (COD), 3-Pentenitrile (3PN), Triisopropylborate (TIPB), Triphenylboron (TPB)

PROJECT NUMBER: 2231/0007

SPONSOR: INVISTA S.a.r.l
INVISTA Building
4123 East 37th Street North
Wichita
KS 67201
UNITED STATES OF AMERICA

PAGE 5:

8. STUDY DESIGN

Dose Groups: On the basis of a range-finding study the dose levels have been selected as follows:

GROUP	DOSE LEVEL (mg/kg/day)	TREATMENT VOLUME (ml/kg)	DURATION OF TREATMENT
Control	0*	4	Up to 54 Days
Low	50	4	Up to 54 Days
Intermediate	175	4	Up to 54 Days
High	600	4	Up to 54 Days
Recovery Control	0*	4	Up to 54 Days
Recovery High	600	4	Up to 54 Days

* Control animals treated with vehicle alone (Dried Arachis oil)

AUTHORISED FOR SAFEPHARM LABORATORIES LIMITED BY: ..... DATE: 03 August 2006
J S Dalmster Bsc (Hons)
STUDY DIRECTOR

APPROVED FOR SPONSOR BY: ..... DATE: 03 Aug. 2006

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Appendix 21 (continued) Protocol

SAFEPHARM LABORATORIES LIMITED

AMENDMENT TO PROTOCOL

AMENDMENT NUMBER: One

PROTOCOL TITLE: Oral (Gavage) Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in the Rat (OECD 422 1996 With Recovery Groups)

TEST MATERIAL: 1,5-Cyclooctadiene (COD), 3-Pentenitrile (3PN), Triisopropylborate (TIPB), Triphenylboron (TPB)

PROJECT NUMBER: 2231/0007

SPONSOR: INVISTA S.a.r.l
INVISTA Building
4123 East 37th Street North
Wichita
KS 67201
UNITED STATES OF AMERICA

AMENDMENT:

Due to a routine review and update, a number of minor changes have made to this protocol.

The following paragraphs/sentences/sections have been amended:

Page 2

Introduction and Objectives

Third paragraph, first sentence "The work will be performed in compliance with UK GLP standards (Schdule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106 as amended by SI 2004/0064)).

Ireland needs included as a country where these international standards are accepted.

Page 6/7

Chronological Sequence of Study

ii) Prior to the start of treatment and once weekly thereafter, all animals will be subjected to detailed clinical observations, made in an open arena to observe functional/behavioral changes.

iii) One day prior to paring (Day 14), five males and five females, randomly selected from each dose group will be sampled for blood chemistry and haematology.

iv) On Day 15, animals will be paired on a one male: one female basis within each dose group, for a maximum of fourteen days and smearing will commence.

xi) On Day 43, subject to confirmation of successful mating, males will be killed and examined macroscopically.

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 21 (continued) Protocol

Page 7

Functional Observations

The first sentence of this section should read as follows:

'Detailed clinical observations will be performed on all non-recovery test and control group animals before the first exposure and once weekly thereafter'.

Page 8

Bodyweights

The first sentence of this section should read as follows:

Individual bodyweights will be recorded on Day 1 (prior to the start of dosing) and at weekly intervals thereafter.

Food Consumptions

The first sentence of this section should read as follows:

'Male dietary intake will be recorded weekly. Female dietary intake will be recorded weekly prior to mating.

Laboratory Investigations

The first sentence of this section should read as follows:

'Haematological and blood chemical: investigations will be performed on five male and five female, randomly selected from each non-recovery test and control group on Day 14'.

Page 10/11

Organ Weights

Initially, the tissues below from five non-recovery males and five non-recovery females, randomly selected from each group and all recovery animals, will be weighed:

Adrenals	Liver	Heart	Thymus	Epididymides
Kidneys	Ovaries	Brain	Spleen	Teste

In addition, the tissues listed below will be weighed for all remaining animals:

Epididymides	Testes	Ovaries

Page 11

Histopathology

The first sentence of this section should read as follows:

'Samples of the following tissues from the randomly selected five males and five females from each dose groups, and tissues shown in bold from all animals will be preserved in 10% formalin:'

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 21 (continued) Protocol

Page 13

Archive

Statement should read as follows:

Unless instructed otherwise by the Sponsor and with the exception of unprocessed wet tissue samples, all original data and the final report will be retained in the Safepharm archive for five years, after which instructions will be sought as to further retention or disposal. Unprocessed wet tissue samples will be retained for two years prior to disposal.

Page 20

Responsible Personnel

Animal health name should read "J Harvey"
Chemical analysis name should read "P Watson"

These minor changes are considered not to affect the purpose or integrity of the study.

AUTHORISED FOR SAFEPHARM LABORATORIES LIMITED BY: ..... DATE: 03 August 2006
J S Dunster BSc (Hons)
STUDY DIRECTOR

APPROVED FOR SPONSOR BY: ..... DATE: 03 Aug 06

Appendix 21 (continued) Protocol

Deviations to Protocol Documented as File Notes During the Study

9. Observations

Functional Observations

During sensory reactivity at Day 4 *post partum* for all females, startle reflex values were not recorded in error. No animals showed any signs of neurotoxicity during behavioural or clinical observations and therefore this omission was considered not to affect the purpose or integrity of the study.

Amendment One

Laboratory Investigations/Histopathology

The animals used for haematological, blood chemical, extended organ weights and extended histopathological investigations were the first five animals from each group and not five randomly selected animals from each group as stated in the amendment.

Page 1, Addendum and Amendment One

The test material material name should read 1,5-Cyclooctadiene (COD) and not 1,5-Cyclooctadiene (COD) as stated in the Protocol, Addendum and Amendment One.

1,5-CYCLOOCTADIENE (COD): : ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 22 Certificates of Analysis of Diets Used

LabDiet PMI NUTRITION INTERNATIONAL

Return to Certified Analysis Retrieval

Product Code: 5002
Product Desc: CERTIFIED RODENT DIET
Lab Number: L0618574-1
Lot Code: JUN 16 06 1A
Entered: 6/28/2006

Assay	Analysis	Units
PROTEIN	20.8	%
FAT (ACID HYDRO.)	5.6	%
FIBER (CRUDE)	4.37	%
ARSENIC	<0.20	PPM
CADMIUM	0.0569	PPM
CALCIUM	0.9388	%
LEAD	0.232	PPM
MERCURY	LESS THAN 0.025	PPM
PHOSPHORUS	0.7289	%
SELENIUM	0.306	PPM

ORGANOPHOSPHATES	PPM	ORGANOPHOSPHATES	PPM
Diazinon	LESS THAN 0.02	Disulfoton	LESS THAN 0.02
Ethion	LESS THAN 0.02	Malathion	LESS THAN 0.02
Methyl Parathion	LESS THAN 0.02	Parathion	LESS THAN 0.02
Thimet	LESS THAN 0.02	Thiodan	LESS THAN 0.02
Trithion	LESS THAN 0.02		

PESTICIDES AND PCB	PPM	PESTICIDES AND PCB	PPM
Aldrin	LESS THAN 0.02	Alpha-BHC	LESS THAN 0.02
Beta-BHC	LESS THAN 0.02	Chlordane	LESS THAN 0.02
DDE	LESS THAN 0.02	DDT	LESS THAN 0.02
Delta-BHC	LESS THAN 0.02	Dieldrin	LESS THAN 0.02
Endrin	LESS THAN 0.02	HCB	LESS THAN 0.02
Heptachlor	LESS THAN 0.02	Heptachlor Epoxide	LESS THAN 0.02
Lindane	LESS THAN 0.02	Methoxychlor	LESS THAN 0.02
Mirex	LESS THAN 0.02	PCB	LESS THAN 0.15

AFLATOXINS	PPB Aflatoxins	LESS THAN 5

No notes.
For additional information, please contact:
1) Customer Service at (314) 982-1310 -- for assay methodology
2) Dr. Dorrance Haught at (314) 317-5178 -- for nutritional interpretation
3) Richmond, IN Manufacturing Plant at (765) 962-9561 -- all other questions

The term "Less Than" is used to signify the lower limit of quantitation of the procedure under the conditions employed.
The use of the term "Less Than" does not imply that traces of analyte were present.

1,5-CYCLOOCTADIENE (COD): : ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 22 (continued) Certificates of Analysis of Diets Used

LabDiet PMI NUTRITION INTERNATIONAL

Return to Certified Analysis Retrieval

Product Code: 5002
Product Desc: CERTIFIED RODENT DIET
Lab Number: L0613811-3
Lot Code: MAR 12 06 2C
Entered: 3/28/2006

Assay	Analysis	Units
PROTEIN	21.3	%
FAT ACID (HYDRO.)	5.47	%
FIBER (CRUDE)	4.22	%
ARSENIC	LESS THAN 0.2	PPM
CADMIUM	0.0559	PPM
CALCIUM	0.9983	%
LEAD	0.181	PPM
MERCURY	LESS THAN 0.025	PPM
PHOSPHORUS	0.707	%
SELENIUM	0.389	PPM

ORGANOPHOSPHATES	PPM	ORGANOPHOSPHATES	PPM
Diazinon	LESS THAN 0.02	Disulfoton	LESS THAN 0.02
Ethion	LESS THAN 0.02	Malathion	LESS THAN 0.02
Methyl Parathion	LESS THAN 0.02	Parathion	LESS THAN 0.02
Thimet	LESS THAN 0.02	Thiodan	LESS THAN 0.02
Trithion	LESS THAN 0.02		

PESTICIDES AND PCB	PPM	PESTICIDES AND PCB	PPM
Aldrin	LESS THAN 0.02	Alpha-BHC	LESS THAN 0.02
Beta-BHC	LESS THAN 0.02	Chlordane	LESS THAN 0.02
DDE	LESS THAN 0.02	DDT	LESS THAN 0.02
Delta-BHC	LESS THAN 0.02	Dieldrin	LESS THAN 0.02
Endrin	LESS THAN 0.02	HCB	LESS THAN 0.02
Heptachlor	LESS THAN 0.02	Heptachlor Epoxide	LESS THAN 0.02
Lindane	LESS THAN 0.02	Methoxychlor	LESS THAN 0.02
Mirex	LESS THAN 0.02	PCB	LESS THAN 0.15

AFLATOXINS	PPB Aflatoxins	LESS THAN 5

No notes.
For additional information, please contact:
1) Customer Service at (314) 982-1310 -- for assay methodology
2) Dr. Dorrance Haught at (314) 317-5178 -- for nutritional interpretation
3) Richmond, IN Manufacturing Plant at (765) 962-9561 -- all other questions

The term "Less Than" is used to signify the lower limit of quantitation of the procedure under the conditions employed.
The use of the term "Less Than" does not imply that traces of analyte were present.

Appendix 23 Chemical Analysis of Test Material Formulations, Methods and Results

1. METHOD OF ANALYSIS

1.1 Summary

The concentration of 1, 5-Cyclooctadiene (COD) in the test material formulations was determined by gas chromatography (GC) using an external standard technique.

1.2 Samples

The test material formulations were diluted with acetone to give a final, theoretical test material concentration of approximately 0.1 mg/ml.

1.3 Standards

Standard solutions of test material were prepared in acetone at a nominal concentration of 0.1 mg/ml.

1.4 Procedure

The standard and sample solutions were analysed by GC using the following conditions:

GC system	:	Agilent Technologies 5890, incorporating autosampler and workstation
Column	:	DB-17 (30 m x 0.53 mm id x 1 µm film)
Oven temperature program	:	initial 70 °C for 2 mins rate 7 °C/min temp. 100 °C for 0 mins rate 50 °C/min final 250°C for 5 mins
Injection temperature	:	230 °C
Flame ionisation detector temperature	:	250 °C
Injection volume	:	1 µl
Retention time	:	~ 4.2 mins

Appendix 23 (continued) Chemical Analysis of Test Material Formulations, Methods and Results

1.5 Homogeneity Determinations

The test material formulations were mixed thoroughly and samples were taken from the top, middle and bottom of the container, shaking between sampling. Sampling was performed in triplicate.

1.6 Stability Determinations

The test material formulations were sampled and analysed initially and then after storage at approximately +4°C in the dark for fourteen days.

1.7 Verification of Test Material Formulation Concentrations

The test material formulations were sampled and analysed within three days of preparation

2. RESULTS

2.1 Homogeneity of Test Material Formulations

Nominal Concentration (mg/ml)	Sampling Location	Concentration Found (mg/ml)			
		1	2	3	Mean
12.5	Top	11.5	11.5	11.5	11.5
	Middle	11.6	11.6	11.5	11.6
	Bottom	11.5	11.6	11.5	11.6
150	Top	143	145	145	144
	Middle	143	144	142	143
	Bottom	145	143	144	144

2.2 Stability of Test Material Formulations

Nominal Concentration (mg/ml)	Concentration Found Initially (mg/ml)	Concentration Found After Storage for Fourteen Days	
		(mg/ml)	(expressed as % of initial)
12.5	11.5	11.1	97
150	144	144	96

Appendix 23 (continued) Chemical Analysis of Test Material Formulations, Methods and Results

2.3 Verification of Concentration of Weekly Test Material Formulation

Week Number	Nominal Concentration (mg/ml)	Concentration Found	
		(mg/ml)	(expressed as % of nominal)
1	0	ND	-
	12.5	12.8	102
	43.8	44.8	102
	150	154	103
2	0	ND	-
	12.5	12.4	99
	43.8	43.4	99
	150	148	99
3	0	ND	-
	12.5	11.8	95
	43.8	42.6	97
	150	147	98
4	0	ND	-
	12.5	12.5	100
	43.8	44.6	102
	150	153	102
5	0	ND	-
	12.5	12.8	102
	43.8	44.5	102
	150	151	100
6	0	ND	-
	12.5	12.6	101
	43.8	44.4	101
	150	153	102
7	0	ND	-
	12.5	12.4	99
	43.8	44.3	101
	150	149	99

ND = none detected
- = not applicable

Appendix 23 (continued) Chemical Analysis of Test Material Formulations, Methods and Results

3. METHOD VALIDATION

3.1 Linearity

A range of standard solutions covering the concentration range 0 to 0.1657 mg/ml, were prepared and analysed.

The detector response was shown to be linear up to 0.1657 mg/ml.

Standard Concentration (mg/ml)	Peak Area (units)
0.000	0.000
0.0553	$1.660x10^5$
0.0884	$2.672x10^5$
0.1105	$3.325x10^5$
0.1326	$4.008x10^5$
0.1657	$4.987x10^5$
Slope	$3.014x10^6$
Intercept	-33.933
Correlation Coefficient (r)	1.000

The results are presented graphically in Figure 1.

3.2 Specificity

The diluent solvent acetone and a blank Dried Arachis Oil BP(control) were analysed. The results are shown in the following table:

Sample	Concentration Found
Acetone	None detected
Dried Arachis Oil BP (control)	None detected

Analysis of the solvent and a blank Dried Arachis Oil BP (control) produced no signal that interfered with the signal due to the test material.

Appendix 23 (continued) Chemical Analysis of Test Material Formulations, Methods and Results

3.3 Accuracy

Samples of Dried Arachis Oil BP were accurately fortified with known amounts of test material, and analysed:

Fortification (mg/g)	Concentration Found (mg/g)	Recovered (%)	Mean Recovery (%)
4.75	4.75	100	101
4.20	4.30	103	
146	148	101	100
153	152	100	

The analytical method has been considered to be sufficiently accurate for the purpose of this study. The test sample results have not been corrected for recovery.

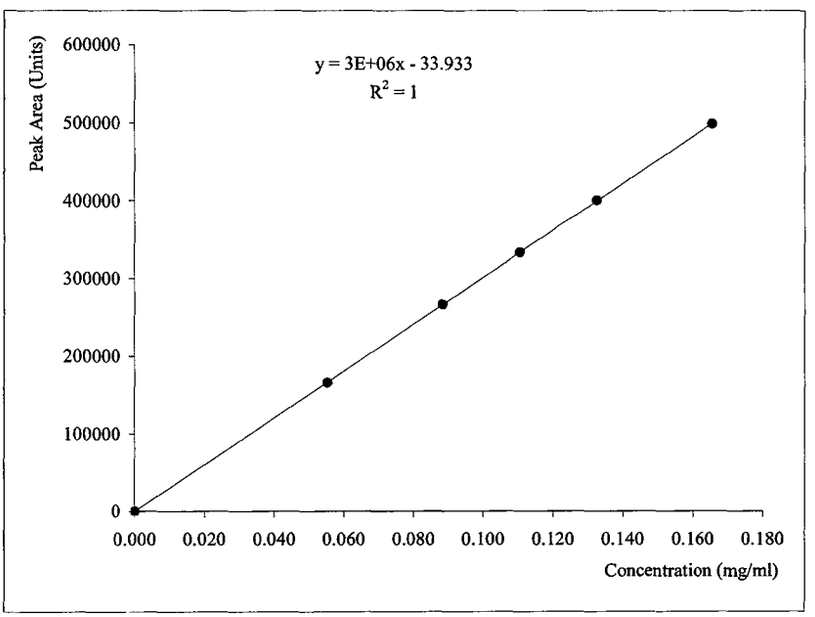
3.3 Conclusion

The analytical method has been satisfactorily validated in terms of linearity, specificity and accuracy for the purposes of the study.

1,5-CYCLOOCTADIENE (COD): : ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 23 (continued) Chemical Analysis of Test Material Formulations, Methods and Results

Figure 1 Linearity of Detector Response

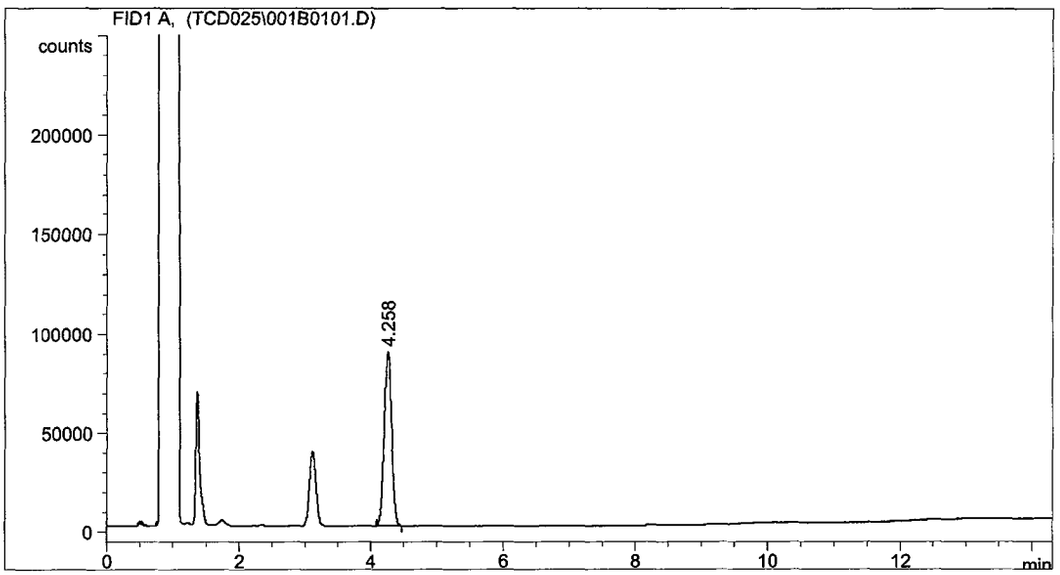


1,5-CYCLOOCTADIENE (COD): : ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

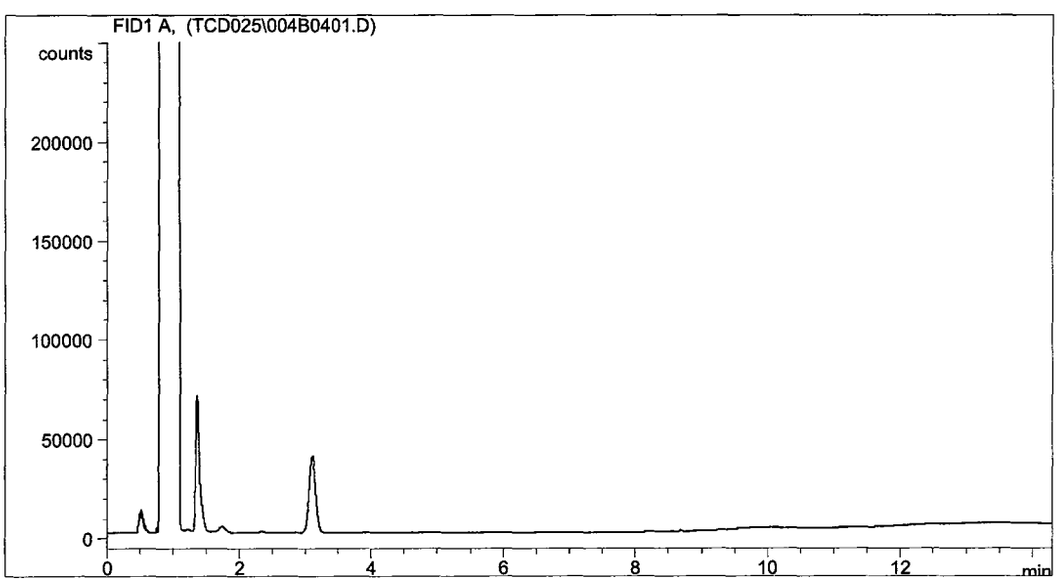
Appendix 23 (continued) Chemical Analysis of Test Material Formulations, Methods and Results

Examples of the typical chromatography generated during this study are given below:

Standard Solution 0.1 mg/ml



Control

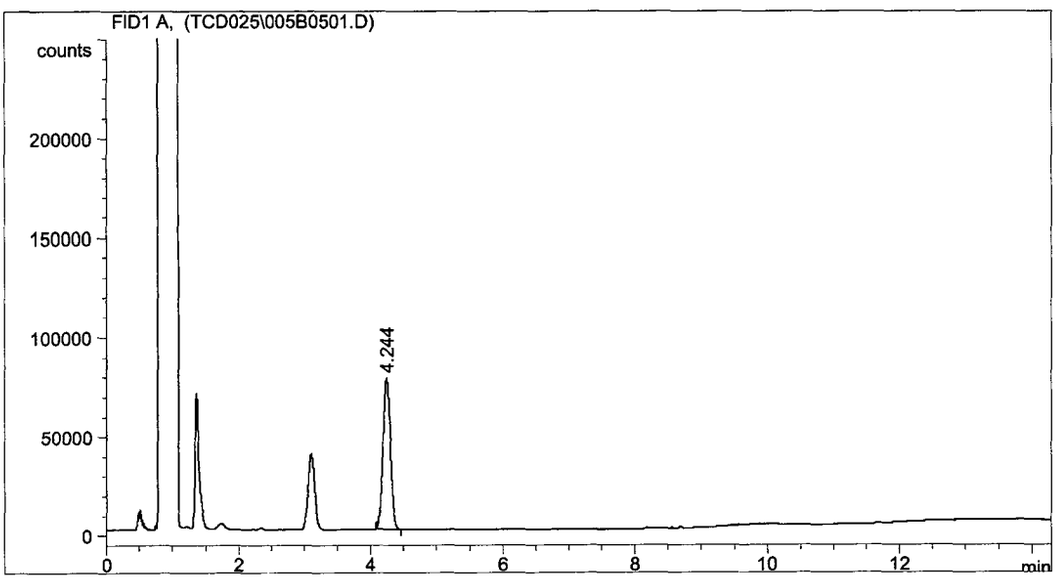


1,5-CYCLOOCTADIENE (COD): : ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

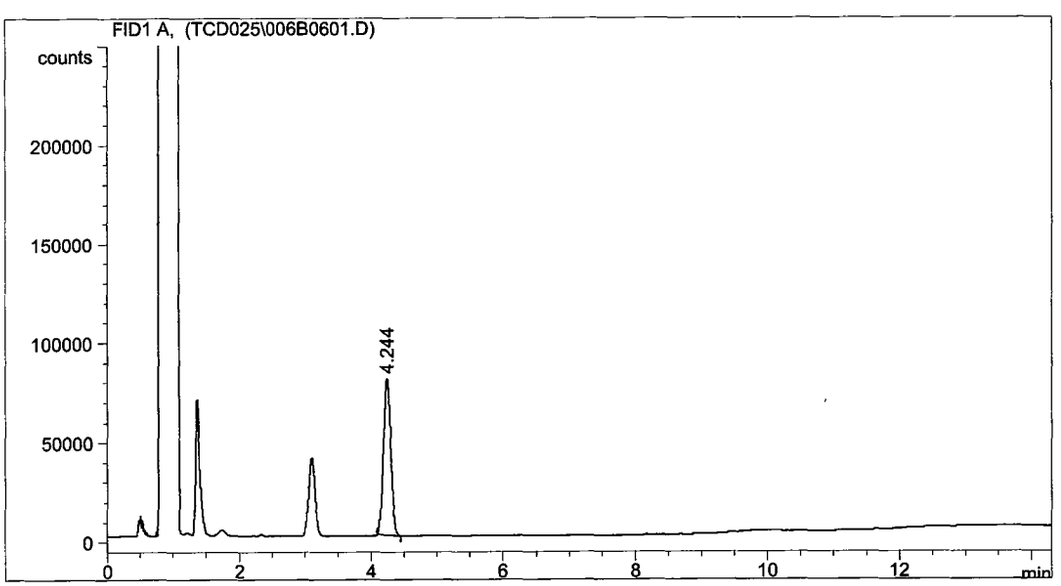
Appendix 23 (continued) Chemical Analysis of Test Material Formulations, Methods and Results

Examples of the typical chromatography generated during this study are given below:

Test Material formulation 12.5 mg/ml



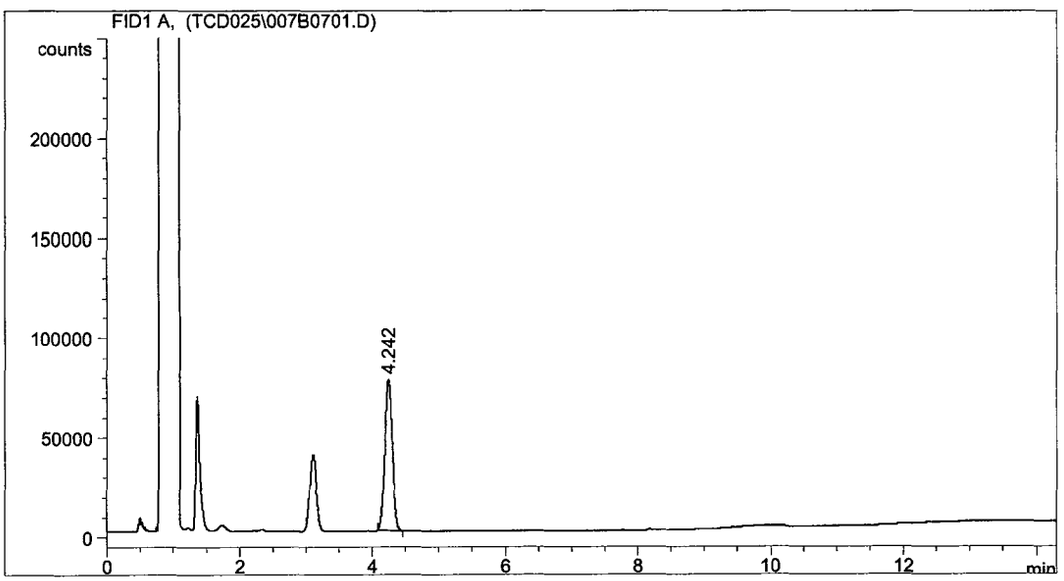
Test Material Formulation 43.8 mg/ml



Appendix 23 (continued) Chemical Analysis of Test Material Formulations, Methods and Results

Examples of the typical chromatography generated during this study are given below:

Test Material Formulation 150 mg/ml



Appendix 24 Laboratory Methods

	UNITS
HAEMATOLOGY	
Parameters measured on potassium EDTA - treated blood:	
Haemoglobin (Hb) - estimated by measurement of cyanmethaemoglobin using the A^c.T5 Diff analyser	g/dl
Total erythrocyte count (RBC) - estimated by the A^c.T5 Diff analyser	10^{12}/l
Haematocrit (Hct) - derived from MCV and RBC by the A^c.T5 Diff analyser	%
Mean Corpuscular Haemoglobin (MCH) - derived from the Hb concentration and RBC by the A^c.T5 Diff analyser	pg
Mean Corpuscular Volume (MCV) - estimated by the A^c.T5 Diff analyser	fl
Mean Corpuscular Haemoglobin Concentration (MCHC) - derived from Hb concentration, RBC and MCV by the A^c.T5 Diff analyser	g/dl
Total leucocyte count (WBC) - estimated by the A^c.T5 Diff analyser	10^9/l
Differential leucocyte count - determined by visual assessment of May-Grünwald/Giemsa stained blood film:	10^9/l
Neutrophils (Neut) Lymphocytes (Lymph) Monocytes (Mono) Eosinophils (Eos) Basophils (Bas)	
Platelet count (PLT) - estimated by the A^c.T5 Diff analyser	10^9/l
Reticulocyte count (Retic) - Brilliant Cresyl Blue slides prepared but count not performed	%
Parameters measured on citrate-treated blood:	
Prothrombin time (CT) - estimated by 'Thrombomax HS' with Calcium Trinity Biotech kit No. T9686	secs
Activated partial thromboplastin time (APTT) – estimated by 'Actin FS' Dade Behring Sysmex Product No. B4218-20 and Bio Mérieux Option 4 coagulometer	secs

1,5-CYCLOOCTADIENE (COD): : ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 24 (continued) Laboratory Methods

	UNITS
BLOOD CHEMISTRY	
Parameters measured on lithium heparin treated blood:	
Urea - estimated by Instrumentation Laboratories reagent kit No. 00182554400 and ILab 600 auto-analyser	mg/dl
Glucose - estimated by Instrumentation Laboratories reagent kit No. 0018250840 and ILab 600 auto-analyser	mg/dl
Total protein (Tot.Prot.) - estimated by Instrumentation Laboratories reagent kit No. 0018251440 and ILab 600 auto-analyser	g/dl
Albumin - estimated by Instrumentation Laboratories reagent kit No. 0018250040 and Instrumentation Laboratories 600 auto-analyser	g/dl
Albumin/Globulin (A/G) ratio = $\frac{\text{albumin}}{\text{total protein} - \text{albumin}}$	
Sodium (Na+) - estimated by ISE electrode No. 0018262400 and Instrumentation Laboratories 600 auto-analyser	mmol/l
Potassium (K+) - estimated by ISE electrode No. 0018263500 and Instrumentation Laboratories 600 auto-analyser	mmol/l
Chloride (Cl-) - estimated by ISE electrode No. 0018263600 and Instrumentation Laboratories 600 auto-analyser	mmol/l
Calcium (Ca++) - estimated by Instrumentation Laboratories reagent kit No. 0018250340 and Instrumentation Laboratories 600 auto-analyser	mmol/l
Inorganic phosphorus (P) - estimated by Instrumentation Laboratories reagent kit No. 0018251240 and Instrumentation Laboratories 600 auto-analyser	mmol/l
Aspartate aminotransferase (ASAT) - estimated by Instrumentation Laboratories reagent kit No. 0018252440 and Instrumentation Laboratories 600 auto-analyser	IU/l
Alanine aminotransferase (ALAT) - estimated by Instrumentation Laboratories reagent kit No. 0018252240 and Instrumentation Laboratories 600 auto-analyser	IU/l
Alkaline phosphatase (AP) - estimated by Instrumentation Laboratories reagent kit No. 0018252140 and Instrumentation Laboratories 600 auto-analyser	IU/l
Creatinine (Creat) - estimated by Instrumentation Laboratories reagent kit No. 0018255540 and Instrumentation Laboratories 600 auto-analyser	mg/dl
Total cholesterol (Chol) - estimated by Instrumentation Laboratories reagent kit No. 0018250540 and Instrumentation Laboratories 600 auto-analyser	mg/dl
Total bilirubin (Bili) - estimated by Instrumentation Laboratories reagent kit No. 0018254640 and Instrumentation Laboratories 600 auto-analyser	mg/dl

1,5-CYCLOOCTADIENE (COD): : ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Appendix 25 Statement of GLP Compliance in Accordance with Directive 2004/9/EC

DH Department of Health

THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE IN ACCORDANCE WITH DIRECTIVE 2004/9/EC

LABORATORY	TEST TYPE
SafePharm Laboratories Ltd. **Shardlow Business Park** **London Road** **Shardlow** **Derby** **DE72 2GD**	**Analytical Chemistry** **Environmental Fate** **Environmental Toxicity** **Mutagenicity** **Phys/Chem Testing** **Toxicology**

DATE OF INSPECTION

30th August 2005

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of the UK GLP Compliance Programme.

At the time of inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

Bryan J Wright 21/11/05.

Mr. Bryan J. Wright
Head, UK GLP Monitoring Authority

PART 2: PRELIMINARY FOURTEEN DAY REPEATED DOSE ORAL (GAVAGE) RANGE-FINDER IN THE RAT

1,5-CYCLOOCTADIENE (COD):

PRELIMINARY FOURTEEN DAY REPEATED DOSE ORAL (GAVAGE) RANGE-FINDER IN THE RAT

1. INTRODUCTION

The range-finder was performed to establish the maximum tolerated dose level (up to 1000 mg/kg/day) of the test material following repeated oral administration to the Sprague-Dawley Crl:CD® (SD) IGS BR strain rat, and to provide information for selection of dose levels for use in this twenty-eight day oral toxicity phase.

2. TEST MATERIAL

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	1,5-Cyclooctadiene (COD)
Description	:	Colourless liquid
Purity	:	99%
Batch number	:	06010MD
Date received	:	12 June 2006/ 21 July 2006 / 10 August 2006
Storage conditions	:	Room temperature in the dark

The integrity of supplied data relating to the identity, purity and stability of the test material is the responsibility of the Sponsor.

2.2 Preparation of Test Material

For the purpose of the range-finder, the test material was prepared as a suspension in Dried Arachis oil. A fresh formulation was made each day and the animals were dosed within three hours of preparation.

The concentration and stability of the test material formulations were not determined analytically.

3. METHODS

3.1 Animals and Animal Husbandry

Fifteen male and fifteen female Sprague-Dawley Crl:CD® (SD) IGS BR strain rats were obtained from Charles River (UK) Limited, Margate, Kent. After an acclimatisation period of at least seven days, animals were selected at random and given a unique number within the range-finder by ear punching.

At the start of treatment the males weighed 130g to 175g and the females weighed 119g to 161g. The animals were housed in groups of three by sex in polypropylene grid-floor cages suspended over trays containing absorbent paper. Free access to mains drinking water and food (Rodent PMI 5002 (Certified) diet, BCM IPS Limited, London, UK) was allowed throughout the range-finder.

The animals were housed in a single air-conditioned room within the Safepharm Barrier Maintained Rodent Facility. The rate of air exchange was at least fifteen air changes per hour and the low intensity fluorescent lighting was controlled to give twelve hours continuous light and twelve hours darkness. Environmental conditions were continuously monitored by a computerised system, and printouts of the mean temperature and humidities were included in the study records. The temperature and relative humidity were controlled to remain within target ranges of 21 ± 2°C and 55 ± 15% respectively.

3.2 Procedure

Five groups, each of six rats (three males and three females) were dosed as follows:

Dose Level (mg/kg/day)	Treatment Volume (ml/kg)	Concentration (mg/ml)
0 (Control)	4	0
150	4	37.5
500	4	125
750	4	188
1000	4	250

The test material was administered daily, for up to fourteen consecutive days, by gavage using a stainless steel cannula attached to a disposable plastic syringe. Control animals were treated in an identical manner with 4 ml/kg/day of Dried Arachis oil.

The volume of test and control material administered to each animal was based on the most recent bodyweight and was adjusted at Days 4, 8 and 11 where applicable.

3.3 Observations

3.3.1 Clinical Observations

All animals were examined for overt signs of toxicity, ill health or behavioural change immediately before dosing and one hour after dosing. All observations were recorded.

3.3.2 Bodyweight

Individual bodyweights were recorded on Days 1, 4, 8, 11 and 15 where applicable or at termination.

3.3.3 Necropsy

On completion of the dosing period, all surviving animals were killed by cervical dislocation and immediately subjected to an internal and external macroscopic examination. Animals that died during the range-finder were also necropsied. No tissues were retained.

3.4 Evaluation of Data

Necropsy data, bodyweights and clinical observations were examined for any adverse effects resulting from treatment.

The data obtained was summarised in tabular form and used to provide the basis for selection of dose levels for the twenty-eight day phase.

4. RESULTS

4.1 Mortality

Animals of either sex treated with 1000 mg/kg/day were killed *in extremis* on Day 2. Animals of either sex treated with 750 mg/kg/day were killed *in extremis* on Day 3. There were no further unscheduled deaths.

4.2 Clinical Observations

A summary incidence of daily clinical observations is given in Table 1 and Table 2.

Animals of either sex treated with 1000 mg/kg/day showed increased salivation, ataxia, laboured respiration, hunched posture, tiptoe gait, ptosis, lethargy, pilo-erection and dehydration by Day 2. Animals of either sex treated with 750 mg/kg/day developed hunched posture, pilo-erection, ptosis and ataxia by Day 2. In addition, by Day 3 animals also showed generalised red/brown fur staining and tiptoe gait. Animals of either sex treated with 500 mg/kg/day showed increased salivation from Day 5 onwards. Increased salivation was also detected in animals of either sex treated with 150 mg/kg/day from Day 11 (males) and Day 13 (females) onwards.

4.3 Bodyweight

Individual bodyweights are given in Table 3.

Animals of either sex treated with 1000 and 750 mg/kg/day showed actual bodyweight losses at termination. No such effects were detected in animals of either sex treated with 500 or 150 mg/kg/day.

4.4 Water Consumption

Daily visual inspections of water bottles revealed no intergroup differences.

4.5 Necropsy

Individual necropsy findings are given in Table 4.

Two males and one female treated with 1000 mg/day showed a reddened non-glandular gastric epithelium. All animals of either sex treated with 750 mg/kg/day showed a distended stomach with one male also showing a pale liver and two males also showing fluid filled small intestines.

No macroscopic abnormalities were detected in animals of either sex treated with 500 or 150 mg/kg/day.

5. CONCLUSION

The dose levels for the main phase of the study were chosen, following consultation with the Sponsor, as:

High dose:	600 mg/kg/day
Intermediate dose:	175 mg/kg/day
Low dose:	50 mg/kg/day

- plus a control group treated with vehicle alone.

TABLES

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 1 Daily Clinical Observations for Males - Summary Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation													
			Day: 1		Day: 2		Day: 3		Day: 4		Day: 5		Day: 6		Day: 7	
			Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h
0 (Control)	3	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
150▲	3	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
500■+	3	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
750	3/0	Ataxia	0	0	0	3	3									
		Hunched posture	0	0	0	3	3									
		Pilo-erection	0	0	0	3	3									
		Ptosis	0	0	0	1	0									
		Red/brown stained ano-genital region	0	0	0	0	1									
		Red/brown stained snout	0	0	0	0	3									
		Death	0	0	0	0	3•									
		No abnormalities detected	3	3	3	0	0									
1000†	3/0	Ataxia	0	0	0	3										
		Dehydration	0	0	0	3										
		Hunched posture	0	0	0	1										
		Ptosis	0	0	0	1										
		Laboured respiration	0	0	0	1										
		Lethargy	0	3	0	0										
		Tiptoe gait	0	0	0	1										
		Death	0	0	0	3•										
		No abnormalities detected	3	0	3	0										

Pre = immediately before dosing
1h = one hour after dosing
■ = increased salivation detected up to ten minutes after dosing - Days 5 to 7 inclusive
† = increased salivation detected up to ten minutes after dosing - Days 1 and 2
• = animals killed *in extremis*
▲ = dark staining on cage tray liners - Days 6 and 7
+ = dark staining on cage tray liners - Day 7 only

Table 1 (continued) **Daily Clinical Observations for Males – Summary Incidences**

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation													
			Day: 8		Day: 9		Day: 10		Day: 11		Day: 12		Day: 13		Day: 14	
			Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h
0 (Control)	3	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
150▲+	3	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
500■+	3	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Pre = immediately before dosing
1h = one hour after dosing
■ = increased salivation detected up to ten minutes after dosing - Days 8 to 14 inclusive
▲ = increased salivation detected up to ten minutes after dosing - Days 11 to 13 inclusive
+ = dark staining on cage tray liners - between Days 8 and 14

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 2 Daily Clinical Observations for Females - Summary Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation													
			Day: 1		Day: 2		Day: 3		Day: 4		Day: 5		Day: 6		Day: 7	
			Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h
0 (Control)	3	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
150	3	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
500■	3	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
750	3/0	Ataxia	0	0	0	3	0									
		Hunched posture	0	0	0	3	3									
		Red/brown stained ano-genital region	0	0	0	0	1									
		Tiptoe gait	0	0	0	0	3									
		Death	0	0	0	0	3•									
		No abnormalities detected	3	3	3	0	0									
1000†	3/0	Ataxia	0	1	0	2										
		Hunched posture	0	0	0	2										
		Lethargy	0	3	0	0										
		Pilo-erection	0	3	0	0										
		Tiptoe gait	0	0	0	2										
		Death	0	0	0	3•										
		No abnormalities detected	3	0	3	0										

Pre = immediately before dosing
1h = one hour after dosing
■ = increased salivation detected up to ten minutes after dosing - Days 5 to 7 inclusive
† = increased salivation detected up to ten minutes after dosing - Days 1 and 2
• = animals killed *in extremis*

Table 2 (continued) Daily Clinical Observations for Females – Summary Incidences

Dose Level (mg/kg/day)	Number of Animals	Clinical Observations	Number Showing Effects At Observation													
			Day: 8		Day: 9		Day: 10		Day: 11		Day: 12		Day: 13		Day: 14	
			Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h	Pre	1h
0 (Control)	3	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
150▲	3	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3
500■	3	No abnormalities detected	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Pre = immediately before dosing
1h = one hour after dosing
■ = increased salivation detected up to ten minutes after dosing - between Days 8 to 14
▲ = increased salivation detected up to ten minutes after dosing - Day 13 only

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 3 Bodyweights - Individual and Group Mean Values

Dose Level (mg/kg/day)	Animal Number and Sex	Bodyweight (g) at Day				
		1	4	8	11	15
0 (Control)	1 M	148	180	216	249	291
	2 M	139	165	202	231	274
	3 M	158	187	225	254	295
	mean	148	177	214	245	287
	4 F	130	142	156	173	185
	5 F	135	146	163	183	196
	6 F	146	162	183	200	221
	mean	137	150	167	185	201
150	19 M	165	179	214	243	282
	20 M	132	153	190	222	268
	21 M	175	179	222	251	294
	mean	157	170	209	239	281
	22 F	119	127	149	159	168
	23 F	161	167	183	190	204
	24 F	123	135	151	164	177
	mean	134	143	161	171	183
500	7 M	150	166	199	228	258
	8 M	160	187	231	266	305
	9 M	139	150	185	214	242
	mean	150	168	205	236	268
	10 F	153	165	191	205	218
	11 F	127	137	160	172	188
	12 F	150	156	183	193	207
	mean	143	153	178	190	204
750	25 M	137	105†	-	-	-
	26 M	136	103†	-	-	-
	27 M	140	106†	-	-	-
	mean	138	105†	-	-	-
	28 F	124	101†	-	-	-
	29 F	131	108†	-	-	-
	30 F	120	97†	-	-	-
	mean	125	102†	-	-	-
1000	13 M	130	115■	-	-	-
	14 M	149	132■	-	-	-
	15 M	154	136■	-	-	-
	mean	144	128■	-	-	-
	16 F	141	124■	-	-	-
	17 F	123	110■	-	-	-
	18 F	137	126■	-	-	-
	mean	134	120■	-	-	-

† = Bodyweights taken on Day 2
■ = Bodyweights taken on Day 3
- = Animal dead

1,5-CYCLOOCTADIENE (COD): ORAL (GAVAGE) COMBINED REPEAT DOSE TOXICITY STUDY WITH REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN THE RAT

Table 4 Necropsy Findings - Individual Observations

Dose Level (mg/kg/day)	Animal Number and Sex	Day of Necropsy	Macroscopic Observations
0 (Control)	1 M	15	No abnormalities detected
	2 M	15	No abnormalities detected
	3 M	15	No abnormalities detected
	4 F	15	No abnormalities detected
	5 F	15	No abnormalities detected
	6 F	15	No abnormalities detected
150	19 M	15	No abnormalities detected
	20 M	15	No abnormalities detected
	21 M	15	No abnormalities detected
	22 F	15	No abnormalities detected
	23 F	15	No abnormalities detected
	24 F	15	No abnormalities detected
500	7 M	15	No abnormalities detected
	8 M	15	No abnormalities detected
	9 M	15	No abnormalities detected
	10 F	15	No abnormalities detected
	11 F	15	No abnormalities detected
	12 F	15	No abnormalities detected
750	25 M	3	Stomach: distended with food Small intestines: fluid filled
	26 M	3	Stomach: distended with food Liver: pale
	27 M	3	Stomach: distended with food Small intestines: fluid filled
	28 F	3	Stomach: distended with food
	29 F	3	Stomach: distended with food
	30 F	3	Stomach: distended with food
1000	13 M	2	Stomach: non-glandular region - reddened
	14 M	2	Stomach: non-glandular region - reddened
	15 M	2	No abnormalities detected
	16 F	2	Stomach: non-glandular region - reddened
	17 F	2	No abnormalities detected
	18 F	2	No abnormalities detected